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Original Communications

FURTHER STUDIES OF THE RELATIONSHIP BETWEEN PULMONARY ARTERIOLAR RESISTANCE AND PULMONARY ARTERY PRESSURES

NOBLE O. FOWLER, JR., M.D.

CINCINNATI, OHIO

IN A previous paper,[1] a study was described of the relationship between the pulmonary vascular resistance and the pulmonary "capillary," pulmonary artery mean, systolic, and diastolic pressures in fifty-four human beings. The purpose of this article is to explore further this problem.

In the preceding communication the correlation between pulmonary resistance and the pulmonary artery systolic, mean, and diastolic pressures was calculated. A high degree of correlation was found in all instances; however, the diastolic pressure exhibited no greater correlation with pulmonary vascular resistance than did the other pressures.

Our present purpose is threefold: first, to study further the interrelationship of these pressures by means of the regression coefficient (to be defined below), which is a better tool than the correlation coefficient, since these measurements are in all probability not normally distributed; second, to determine whether or not any of the pulmonary artery pressures is a significantly better guide to pulmonary vascular resistance than the others; third, to set up equations for estimation of the pulmonary arteriolar resistance from the other pulmonary artery pressure measurements.

MATERIAL

Patients were from the medical wards of the Cincinnati General Hospital. Some were convalescents and others suffered from a variety of heart and lung diseases (Table I). Many of the patients in this study were included in the previous report. A total of thirty-nine were found satisfactory according to criteria described below.

From the Department of Medicine, Cincinnati General Hospital, and the College of Medicine, University of Cincinnati.

Received for publication Jan. 21, 1953.

TABLE I

PATIENT, AGE, SEX, DISEASE	PULMONARY "CAPILLARY" MEAN PRESSURE, MM. HG	PULMONARY ARTERY PRESSURE, MM. HG		CARDIAC OUTPUT, L/MIN.		PULMONARY ARTERIOLAR RESISTANCE, DYNES SEC./CM.$^{-5}$	ARTERIAL O_2 SAT., % OF CAPACITY
		MEAN	SYSTOLIC/ DIASTOLIC	INDEX	TOTAL		
1. B. M. (F, 57) Bronchiectasis	9	29	38/17	2.7	4.0	397	84.1
2. I. W. (F, 29) Post-partum myocardosis	18	25	37/15	3.3	4.9	114	94.2
3. S. J. (M, ?68) HCVD, no failure	14	25	36/20	2.3	4.5	202	94.7
4. C. C. (M, 46) Normal (conv. empyema)	12	17	25/11	2.8	5.0	74	90.3
5. J. S. (M, 75) Hypertension	22	26	39/22	2.6	4.3	89	93.5
6. J. B. (M, 63) Carcinoma of lung	15	26	36/21	2.7	4.2	202	94.4
7. O. B. (M, 37) Conv. pneumonia	7	15	26/9	3.2	5.5	106	89.4
8. G. A. (M, 59) Cor pulmonale Diaphragmatic hernia	18	45	61/35	2.9	4.9	452	75.5
9. M. S. (M, 49) Mitral stenosis	23	54	70/30	2.0	3.7	666	86.5
10. M. B. (M, 60) HCVD, silicosis	7	18	27/14	2.3	4.2	213	96.1
11. P. S. (M, 43) Malnutrition	4	10	18/7	3.7	5.9	85	99.3
12. W. B. (M, 37) Conv. pleurisy	7	13	21/9	4.5	8.0	62	89.6
13. C. M. (M, 49) Rheumatoid arthritis	7	18	26/9	3.0	5.1	170	90.3
14. J. S. (M, 39) Hemoptysis ? cause	7	19	32/10	2.6	4.8	189	83
15. L. J. (M, 20) Fibrosis lung	14	27	36/21	3.0	7.3	133	92.7
16. L. A. (M, 43) Neuritis, malnutrition	9	14	24/9	4.3	7.9	47	93.1
17. H. H. (M, 39) Paresis	9	15	16/7	3.0	4.9	83	95.6
18. G. Y. (M, 46) Conv. pneumonia	11	17	24/13	2.3	4.3	113	94.1
19. H. P. (M, 48) CNS syphilis	6	16	23/11	3.0	5.4	142	94.1
20. C. H. (F, 49) Paresis	8	20	23/10	3.4	5.8	160	96.3

TABLE I (CONT'D)

PATIENT, AGE, SEX, DISEASE	PULMONARY "CAPILLARY" MEAN PRESSURE, MM. HG	PULMONARY ARTERY PRESSURE, MM. HG		CARDIAC OUTPUT, L/MIN.		PULMONARY ARTERIOLAR RESISTANCE, DYNES SEC./CM.$^{-5}$	ARTERIAL O_2 SAT., % OF CAPACITY
		MEAN	SYSTOLIC/ DIASTOLIC	INDEX	TOTAL		
21. S. M. (M, 40) Conv. pneumonia	7	14	21/9	3.1	5.2	101	96.5
22. D. C. (M, 46) Heart disease ? cause	11	28	44/16	2.5	4.6	295	89
23. M. L. (F, 52) Emphysema	6	21	34/16	2.4	3.6	337	89.3
24. O. M. (M, 39) HCVD, failure	17	35	50/29	1.5	2.4	593	94.9
25. A. B. (M, 46) Comp. HCVD, syphilis, optic atrophy	12	22	36/14	3.9	7.8	102	95
26. G. A. (M, 60) Cor pulmonale	19	74	119/51	1.8	3.3	1331	55.2
27. C. G. (M, 66) Normal heart, frontal lobe atrophy	6	14	23/7	3.0	5.5	126	91.9
28. W. E. (M, 56) Carcinomatous lung, multiple myeloma	16	35	52/28	3.7	5.9	256	73.7
29. J. M. (M, ?47) Pneumonia, carcinomatous lung	8	12	22/7	3.6	5.7	53	90.8
30. G. Y. (M, 48) Normal	6	17	24/8	4.7	8.9	104	92.2
31. F. T. (M, 52) Metastatic carcinomatous lung	6	25	36/14	3.3	5.6	270	91.6
32. J. B. (M, 53) Emphysema, cor pulmonale	12	34	55/20	3.2	5.5	321	78.1
33. H. S. (M, 51) Emphysema	6	32	64/17	3.2	4.8	415	85.6
34. C. D. (M, 26) Eisenmenger's complex	9	102	140/80	2.1	3.99	1863	84.8
35. I. E. (F, 25) Mitral stenosis, postoperative	14	30	45/21	2.9	3.8	349	96
36. W. B. (M, 17) Normal	7	16	27/10	3.3	6.1	118	98
37. R. L. (M, 21) Normal	13	18	26/14	2.6	4.7	86	93.7
38. M. H. (F, 30) Mitral stenosis, postoperative	18	27	49/22	1.7	2.5	288	97
39. O. M. (M, 39) HCVD failure	17	34	50/24	1.5	2.4	557	94.9

METHODS

The studies were performed as described previously.[1] Subjects were studied in the fasting state, sedated by 0.1 Gm. of Seconal. Cardiac venous catheterization was done according to Cournand and Ranges.[2] Cardiac outputs were measured by the direct Fick method. Pressures were recorded by the Hathaway optical oscillograph. Pulmonary "capillary" pressures were obtained in the manner of Hellems and co-workers.[3]

Pulmonary arteriolar resistance was calculated from the formula

$$R = \frac{PA - PC}{CO} \times 1332$$

Where R = Pulmonary arteriolar resistance in dynes sec./cm.$^{-5}$
PA = Mean pulmonary artery pressure mm. Hg
PC = Mean pulmonary "capillary" pressure mm. Hg
CO = Cardiac output in c.c./sec.

RESULTS

The results of pressure measurements, determination of cardiac output and calculation of the pulmonary arteriolar resistance are shown in Table I. Patients were included in this study only if oxygen consumption fell within the basal range given by Aub and Dubois[4] allowing an occasional fall of 10 per cent below this range because of heavy sedation. A total of thirty-nine patients were satisfactory according to this criterion.

After the graph had shown that one of the pairs of variables was distributed at random about the other in linear fashion, calculations of the regression coefficients were made as follows:

$$byx_1 = \frac{S\{y\,(x_1 - \bar{x}_1)\}}{S\{(x_1 - \bar{x}_1)^2\}} \qquad byx_3 = \frac{S\{y\,(x_3 - \bar{x}_3)\}}{S\{(x_3 - \bar{x}_3)^2\}}$$

$$byx_2 = \frac{S\{y\,(x_2 - \bar{x}_2)\}}{S\{(x_2 - \bar{x}_2)^2\}} \qquad byx_4 = \text{etc.}$$

Where y = pulmonary arteriolar resistance
x_1 = pulmonary "capillary" pressure
x_2 = pulmonary artery mean pressure
x_3 = pulmonary artery systolic pressure
x_4 = pulmonary artery diastolic pressure
$\bar{x}_1$ = mean of x_1 etc.
byx_1 = regression coefficient of pulmonary arteriolar resistance on pulmonary "capillary" pressure
byx_2 = regression coefficient of pulmonary arteriolar resistance on pulmonary artery mean pressure
byx_3 = regression coefficient of pulmonary arteriolar resistance on pulmonary artery systolic pressure
byx_4 = regression coefficient of pulmonary arteriolar resistance on pulmonary artery diastolic pressure

From these formulas, the following values were obtained:

$$byx_1 = 18.8$$
$$byx_2 = 19.2$$
$$byx_3 = 13.3$$
$$byx_4 = 24.1$$

The significance of these values was determined from these formulas

$$s^2e = \frac{S\,(y - \bar{y})^2 - b\,S\,(x - \bar{x})\,(y - \bar{y})}{D.F.}$$

$$s^2b = \frac{s^2e}{S\,(x - \bar{x})^2}$$

$$t = \frac{b}{sb}$$

Where D.F. = n-2

s^2e = variance of the estimate
s^2b = variance of b

From these calculations the following data were obtained:

$$t_1 = 1.71;\ p = > 0.05$$
$$t_2 = 20.65;\ p = < 0.001$$
$$t_3 = 19.00;\ p = < 0.001$$
$$t_4 = 16.39;\ p = < 0.001$$

From these values it may be seen that there is a highly significant association between the pulmonary arteriolar resistance and each of the following: pulmonary artery mean pressure, pulmonary artery systolic pressure, and pulmonary artery diastolic pressure. Of these three the association is least in the case of the pulmonary artery diastolic pressure. The association with pulmonary "capillary" pressure is not significant.

Our next task was to ascertain whether the difference in association shown by the above regression coefficients is statistically significant. The variance was estimated as follows:

$$S_1^2 = \frac{1}{n\text{-}2}\,S\,(y^2) - \bar{y}S(y) - byx_1S\,\{y\,(x_1 - \bar{x}_1)\}$$

$$S_2^2 = \frac{1}{n\text{-}2}\,S\,(y^2) - \bar{y}S(y) - byx_2S\,\{y\,(x_2 - \bar{x}_2)\}$$

etc.

$$S_1^2 = 117{,}026$$
$$S_2^2 = 9{,}794$$
$$S_3^2 = 11{,}758$$
$$S_4^2 = 14{,}998$$

The measurement with the least variance (S_2^2) is the most accurate. However, it must be determined whether the difference between S_2 and S_1, S_3, and S_4 is significant:

$$\frac{S_1^2}{S_2^2} = 11.949 \qquad \frac{S_4^2}{S_2^2} = 1.531$$

$$\frac{S_1^2}{S_3^2} = 9.953 \qquad \frac{S_4^2}{S_3^2} = 1.276$$

$$\frac{S_1^2}{S_4^2} = 7.803$$

$$\frac{S_3^2}{S_2^2} = 1.201$$

The significance of these ratios was determined from the following formulas:[5]

$$z = \tfrac{1}{2} \log_e \frac{S_2^2}{S_1^2} = \tfrac{1}{2} \{\log_e S_2^2 - \log_e S_1^2\}$$

$$\sigma z = \sqrt{\tfrac{1}{2} (1/n_1 - 1/n_2)}$$

$$\frac{z}{\sigma z} = \frac{\tfrac{1}{2} \log_e \frac{S_2^2}{S_1^2}}{\sqrt{\frac{1}{37}}}$$

for $p = 0.01$, $z/\sigma z = 2.575829$. {Normal distribution table[6]}

$$\log_e \frac{S_2^2}{S_1^2} = \frac{2.575829}{3.041} = 0.84703$$

$$\frac{S_2^2}{S_1^2} = 2.337$$

for $p = 0.05$ $\frac{S_2^2}{S_1^2} = 1.9051$ {Normal distribution table[6]}

From the previous ratios of S_1^2, S_2^2, S_3^2, S_4^2 it may be seen that pulmonary artery systolic, diastolic, and mean pressures are each significantly better measures of the pulmonary arteriolar resistance than is the pulmonary "capillary" pressure; although the pulmonary artery mean pressure appears to be a better measure of pulmonary artery resistance than the other measurements, it is not significantly so.

The regression equation used is:

$Y = \bar{y} + b(x - \bar{x})$

$Y = bx + (\bar{y} - b\bar{x})$

Where Y = calculated value of dependent variable.

This may be used for calculating pulmonary arteriolar resistance from pulmonary artery mean pressure,

$Y_2 = 19.2\, x_2 + 288.8 - (19.2 \cdot 26.6)$

$Y_2 = 19.2\, x_2 - 222.7$

Where x_2 = observed mean pulmonary artery pressure.

The sampling variance of Y_2, $S^2_{Y_2}$ was calculated from the formula:

$$S^2_{Y_2} = S^2_e \left\{ \frac{1}{n} + \frac{(x_2 - \bar{x}_2^{\,2})}{S\,(x - \bar{x})^2} \right\}$$

The standard error of Y_2, $S_{Y_2} = \sqrt{257.4 + 0.86\ (x_2 - 26.6)^2}$

Similarly, for determining resistance from systolic pressure:

$Y_3 = 13.3x_3 - 241.9$ where x_3 = observed systolic pressure

$S_{Y_3} = \sqrt{298.4 + 0.49\ (x_3 - 39.9)^2}$

For determining resistance from diastolic pressure:

$Y_4 = 24.1x_4 - 147.4$

$S_{Y_4} = \sqrt{389.7 + 2.15\ (x_4 - 18.1)^2}$ where x_4 = observed diastolic pressure.

From the foregoing, the following statements may be made. There was found to be a high degree of association between pulmonary arteriolar resistance and each of these: pulmonary artery systolic pressure, pulmonary artery diastolic pressure, and pulmonary artery mean pressure. In the patients studied, pulmonary resistance could be estimated from any one of these pressures from regression equations, but not with precision, since there is considerable scatter about the regression line.[1] The data suggest that the diastolic pressure is a less reliable guide to the pulmonary vascular resistance than is either the mean or systolic pressure, but there is not a significant difference in the accuracy of any of the three pressures as a guide to pulmonary vascular resistance. This statement agrees with the previous conclusion.[1]

The conclusions drawn above with regard to the relationships between the various pulmonary artery pressures and pulmonary arteriolar resistance should be limited to situations similar to those obtaining in the subjects studied and to the ranges of pulmonary pressures in these subjects. As shown by Warren and Doyle,[7] rapid saline infusion in human beings produces a comparable increase in both pulmonary artery and pulmonary "capillary" pressure. We[8] have found that infusion of norepinephrine produces a rise in both pulmonary artery and pulmonary "capillary" pressure of human beings. Dexter and coworkers[9] have shown that in the presence of increased pulmonary artery flow associated with atrial septal defect or patent ductus arteriosus there may be pulmonary hypertension without an increase in pulmonary arteriolar resistance. However, patients with increased pulmonary arteriolar resistance were excluded from the group studied by Dexter. In the three conditions mentioned above, no association between pulmonary arteriolar resistance and pulmonary artery mean, systolic, or diastolic pressures would be found. These conditions were not present in any of the group included in the present study.

Although we have studied normal subjects along with those suffering from chronic lung disease, left heart failure, and mitral stenosis, our graphs show no difference between these groups with regard to association between pulmonary arteriolar resistance on the one hand and the various pulmonary artery pressures and pulmonary "capillary" pressure on the other. In particular, we found no constant relationship between the level of pulmonary "capillary" pressure and the height of pulmonary arteriolar resistance in mitral stenosis and in left heart failure. This has been true in cases studied since these calculations were made. We studied recently two cases of mitral stenosis, each of whom had a pulmonary "capillary" pressure of 23 mm. mercury. In one patient, the pulmonary arteriolar resistance was 1193 dynes sec./cm.$^{-5}$; in the other, the pulmonary arteriolar resistance was 130 dynes sec./cm.$^{-5}$ In this respect, our findings are

similar to those of Lukas and Dotter.[10] Dexter and co-workers[9] have demonstrated that in mitral stenosis and left heart failure the pulmonary arteriolar resistance tends to remain unchanged until the pulmonary "capillary" pressure reaches about 20 to 25 mm. mercury; at this point, the pulmonary arteriolar resistance tends to increase. It should be stressed, as mentioned by Dexter and as exemplified by the two instances cited above, that the relationship between pulmonary "capillary" pressure and pulmonary arteriolar resistance is not linear even at higher levels of pulmonary "capillary" pressure.

It should be added that our failure to find a significant association between pulmonary "capillary" pressure and pulmonary arteriolar resistance in the group as a whole or in mitral stenosis or left ventricular failure in particular does not justify the conclusion that no relationship exists. Study of a larger group of patients or of a condition not included in those studied might well demonstrate some relationship.

SUMMARY AND CONCLUSION

In thirty-nine human beings, some normal, and others having a variety of heart and lung diseases, a study was made of the relationship between pulmonary artery mean, systolic, and diastolic pressures on the one hand, and pulmonary arteriolar resistance on the other. A highly significant relationship was found between resistance and each of the three pressures. Regression equations for estimating pulmonary arteriolar resistance from pulmonary artery systolic, diastolic, or mean pressure are given. It is stressed that conclusions concerning these associations should be limited to the conditions represented by the material studied. The pulmonary "capillary" pressure showed no significant association with pulmonary arteriolar resistance in the studies reported here.

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THE DURATION OF THE Q-U INTERVAL AND ITS COMPONENTS IN ELECTROCARDIOGRAMS OF NORMAL PERSONS

EUGENE LEPESCHKIN, M.D., AND BORYS SURAWICZ, M.D.

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IN A recent paper[5] the authors emphasized the difficulties encountered in the exact determination of the end of the T wave and, hence, of the Q-T duration. These difficulties were especially great in cases which showed complete or partial superposition of the T and U waves. In many such cases the only points of reference which could be identified with certainty were the apices of the T wave and/or U wave and the onset of the second heart sound. It was thought that in such cases the end of the T wave could be determined indirectly by using these points of reference. For this purpose, it was necessary to study the normal relation of these points to the end of the T wave. On the other hand, it has been observed repeatedly that some factors may have a selective influence on the duration of certain components of the Q-T interval, such as the duration of the RS-T segment. As this duration has not been defined and measured exactly, it became necessary to carry out such measurements in a large number of normal persons and to determine the relation of this value to other components of Q-T. It was also of interest to determine the duration of the interval from the beginning of QRS to the apex and end of the U wave in its relation to the heart rate, which had not been determined heretofore. It was hoped that a correlation of this duration to the duration of the mechanical activity of the heart might also shed some light on the nature of the U wave.

METHOD OF STUDY

The Q-U interval was subdivided into a number of components of which some, such as the Q-T duration, had already been the objects of considerable study.[1] For other components it was necessary to devise an exact method of measurement and to invent a new nomenclature. As a further development of the nomenclature used by Hafkesbring and Ashman,[2] the apex of a wave was designated by the letter connoting this wave, accompanied by the small letter "a". In order to prevent confusion with the already existing symbol "Ta" to denote the T wave of the atrium,[1] it was decided to use "aT" and "aU" to designate the apices of the T and U waves, respectively. The end of the RS-T segment or the origin of the T wave was called, accordingly, the point "oT" of the electrocardiogram. The duration of the interval from the beginning of QRS to

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the points just mentioned was called the Q-oT, Q-aT, and Q-aU duration. According to this principle the duration from the beginning of QRS to the end of the T or U wave would be designated as the Q-eT and Q-eU durations, but in order to preserve the existing electrocardiographic nomenclature we have preferred to use the terms "Q-T duration" and "Q-U duration" instead.

As described in a previous article,[3] we have used the earliest point of the QRS complex in synchronous leads as our point "Q", which served as the point of reference for all measurements. The first component measured was the duration of the QRS complex. In determining the end of this complex, the method of the mid-point of the RS-T junction was used, as described in a previous article.[3] Because the QRS duration was measured from the earliest point to the latest point of QRS in synchronous limb and chest leads, the values obtained are higher than those given in previous publications, where nonsynchronized standard limb leads were used.[3]

The next component measured was the duration from the beginning of QRS to the end of the RS-T segment or the *Q-oT duration*. In cases where the RS-T segment is straight and forms a definite angle with the initial limb of the T wave this point is easy to determine. In most cases, however, the RS-T segment shows a more or less gradual transition into the T wave. In these cases the point of origin of the T wave was considered as the point on the RS-T segment most distant from a line connecting the peak of the T wave with the RS-T junction (Fig. 1). In most cases it was not necessary to actually draw the line; instead, the tracing was held so that the RS-T junction and the apex of the T wave were on the same horizontal level and the lowest point of the RS-T segment was then easily discernible. In limb leads the measurements were made in the lead showing the highest voltage of the T waves. Other leads with upright or inverted T waves usually showed similar Q-oT values in a given case, but leads with small diphasic T waves usually gave shorter values and were not used for measurement. In the precordial leads, leads from the transitional zone (V_{1-3}) often showed T waves which were diphasic or had a terminal isoelectric component; these leads usually had a considerably shorter RS-T segment and were not used for measurement even if the T waves were higher in these leads than in leads further to the left. Therefore, the measurements were made in Leads V_{4-6}, in which the point oT almost always coincided exactly with the same point as determined in the limb leads (Fig. 1 of our previous paper[5]).

Ashman[4] considered the RS-T segment as the section of the curve following QRS during which the trace remains on the line of zero potential in all three leads. According to our experience, the RS-T segment of normal persons never remains completely on the line of zero potential in all leads for any length of time. Ashman actually found an RS-T segment of zero duration in many normal persons, but he also describes durations up to 0.17 second in normal cases. Therefore, he must have deviated from his strict definition of the RS-T segment in making his measurements and must have used some other practical criteria to determine the end of this segment. We could not find a description of these criteria in his book and were forced, therefore, to develop our own criteria.* Our values, accordingly, cannot be compared with those of Ashman.

*According to a verbal statement made by Dr. R. Ashman to one of the present authors (E.L.) in December, 1952, he now considers that his earlier measurements of the RS-T segment were not sufficiently objective to be of practical value in electrocardiography.

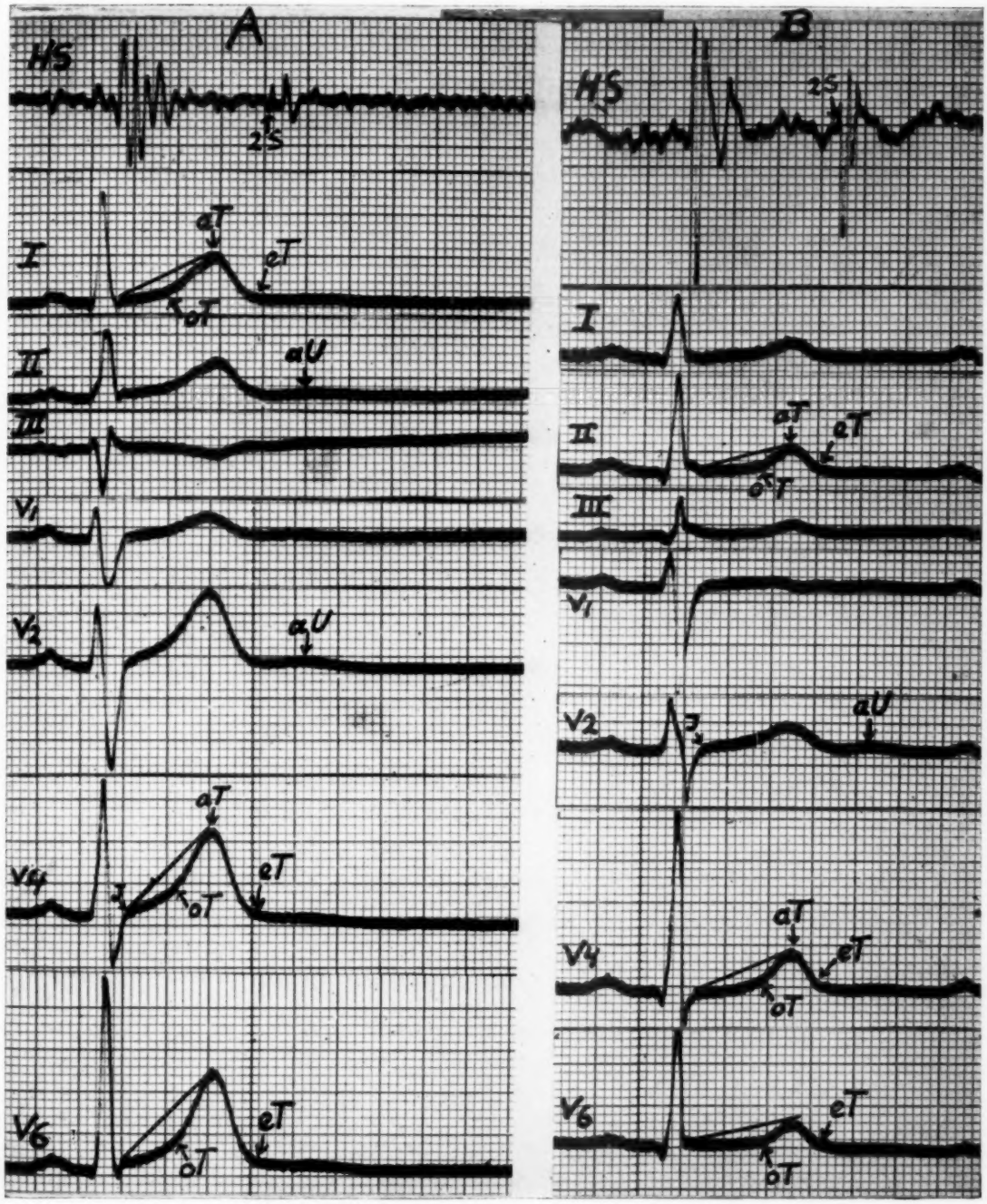

Fig. 1.—Electrocardiograms of normal persons illustrating the technique of measurement. *A*, 22-year-old man. *B*, 28-year-old woman. Leads I to III and the heart sounds, as well as Leads V_1, V_2, V_4, and V_6 are synchronous. The points used for measurement are designated with the corresponding symbols. Time lines are 0.02 and 0.10 second apart (double paper speed).

In order to measure the relative steepness of the RS-T segment, the duration from the beginning of QRS to the point on this segment when one-half of the height of the T wave is reached was measured and expressed as a percentage of the Q-T duration.[1] The practical method of measurement was to bisect the distance between the level of the apex of T and the level of the beginning of QRS and to determine the point where this new level intersects the RS-T segment. We shall designate this point as the "half-way point" of T, and the time from the beginning of QRS to this point as the "*Q-T/2 interval.*" In this paper this interval was expressed as a percentage of the Q-T duration, but it could be used also as an absolute value or expressed as a percentage of the Q-aT duration.

The *Q-aT interval* was measured always to the point on the T wave most distant from the base line; this point could be recognized easily in all cases. As in the case of the Q-oT duration, the measurements in the limb leads were made in the lead with the highest T waves. In the precordial leads, leads from the transitional zones (V_{1-3}) showing T waves of diphasic form or having an isoelectric terminal portion were not used in the determination of the Q-aT duration. The point aT thus corresponded with the apex of the T-loop of the vectorcardiogram.

In the measurement of the *Q-T interval*, there were two possibilities of determining the end of the T wave. If there was an isoelectric interval between T and U, the point at which the T wave approached this interval completely was taken as the end of T. If there was partial fusion of T and U, the sudden change of slope (notch or kink) between T and U was used to define the end of T, as outlined in a previous article.[5] The lead with the longest Q-T interval was used.

The *Q-aU interval* was always determined in the lead which showed the purest positive monophasic U waves. This was usually the lead V_2 or V_3 and did not coincide with the lead used for measurement of the T-wave intervals. The point of the U wave most distant from the base line was defined as the apex of U. At high heart rates the U wave showed superposition of the P wave of the following heart beat; in these cases the apex of U could be determined only approximately and in some cases it was impossible to determine it.

The *Q-U interval* was also measured in the lead showing the highest and the most purely monophasic positive U waves. The point where the U wave completely reached the base line was considered as the end of U. Because of the very gradual termination of U and of the unavoidable spontaneous oscillations of the base line, this point could be determined only approximately in the majority of the cases. The determination was difficult especially at high heart rates, where the end of U was masked, more or less completely, by the P wave and the P-Ta segment of the following heart beat. In such cases an attempt was made to reconstruct the course of the U wave by connecting the beginning and the end of the P wave.

The heart sounds were registered with a magnetic microphone with a small piece of cork pasted on its membrane and placed in direct contact with the skin. The frequency response of the microphone plus recording and amplifying system was approximately 5 to 200 cycles per second. The microphone was placed at the left second intercostal space near the sternum over the aortic valves.

The interval *Q-second heart sound* or *Q-2S* was measured to the beginning of the rapid vibrations of this sound. In almost all cases these vibrations had a very high frequency and caused an almost vertical line to be registered on the tracing. The beginning of this line was used for measurement. In a few cases even the fastest vibrations of the second heart sound had a visible slope; in these cases the kink between the first of these fast vibrations and the slow vibrations preceding them was used for measurement.

For the purpose of this study, fifty men and fifty women were selected. These were summer session students at the University of Vermont who considered themselves as completely healthy and in whom the history and a physical examination of the heart and blood vessels revealed no abnormalities. The electrocardiogram at rest and after the double Master two-step exercise test was normal according to the accepted standards. The electrocardiogram was taken in the recumbent position after a period of adequate rest. The three standard leads and the precordial Leads V_1, V_2, V_4, and V_6 were registered synchronously with the heart sounds by means of the Sanborn four channel direct-writing electrocardiograph "Poly-Viso."

As the heart rate is one of the most important factors influencing the duration of the various components of ventricular electrical activity, all the measurements were first correlated with the R-R interval (Fig. 2). A smoothed curve of the mean values was obtained separately for men and women. To determine the influence of age, the average ages of all persons having values situated above and below the mean were determined for each sex. In the case of the QRS duration this procedure was applied in respect to the weight and height.

RESULTS

The duration of *QRS* ranged from 0.075 to 0.12 second. The average for men was 0.098 second and that for women was 0.092 second. Ten per cent of the men but none of the women had values of 0.12 second, while 6 per cent of the men and 26 per cent of the women had values of 0.08 second and less. This difference between men and women could be due to the fact that the men showed a slower average heart rate than the women. However, the same difference was present at all heart rates; at R-R intervals of 60 to 80 the mean for men was 0.095 second, while that for women was 0.090 second. On the other hand, at R-R intervals between 80 and 1.00 second the means were 0.10 second for men and 0.094 second for women.

Another factor which could be responsible for the difference in the duration of QRS in men and women is the heart size. Unfortunately, it was impossible to measure the heart size in all cases, but it was thought that the body weight or body size may offer an indirect indication of the heart size. The average weight of women having a QRS duration above the mean for a given rate was 143 pounds, while the average weight of those below the mean was 137 pounds. The average weight of the men having greater than average values was 165 pounds while in those having smaller than average values it was 178 pounds. This indicates that within each sex there is no definite relation between body weight and QRS duration.

The relation between the duration of QRS and the height was much more definite than that between QRS and the weight. In women the mean was 0.082 second for a height of 5 feet, 0.092 second for 5 feet 4 inches and 0.102 second at 5 feet 8 inches. In the case of the men, the mean had a value of 0.092 second for the lowest height of 5 feet 4 inches, as can be seen from Fig. 2; it increased from 0.082 second for a height of 5 feet to 0.118 second for a height of 6 feet 4 inches. The means for men and women of the same height brackets were identical. This indicates that the sex difference in the duration of QRS in the present group was due entirely to differences in the height

and presumably in the heart size. That no definite relationship could be found to the weight could be explained by the fact that in this series the women and the shorter men tended to be overweight more often than did the taller men. In addition to the size of the heart, the fact that taller persons tend to have lower heart rates may be responsible for part of the increased duration of QRS in these persons. In this series, the average R-R interval of women below 5 feet 4½ inches was 0.80 second while that of women above this height was 0.88 second. Correspondingly, the average R-R interval of men below 5 feet 9½ inches was 0.80 second while in men above this height it was 0.71 second.

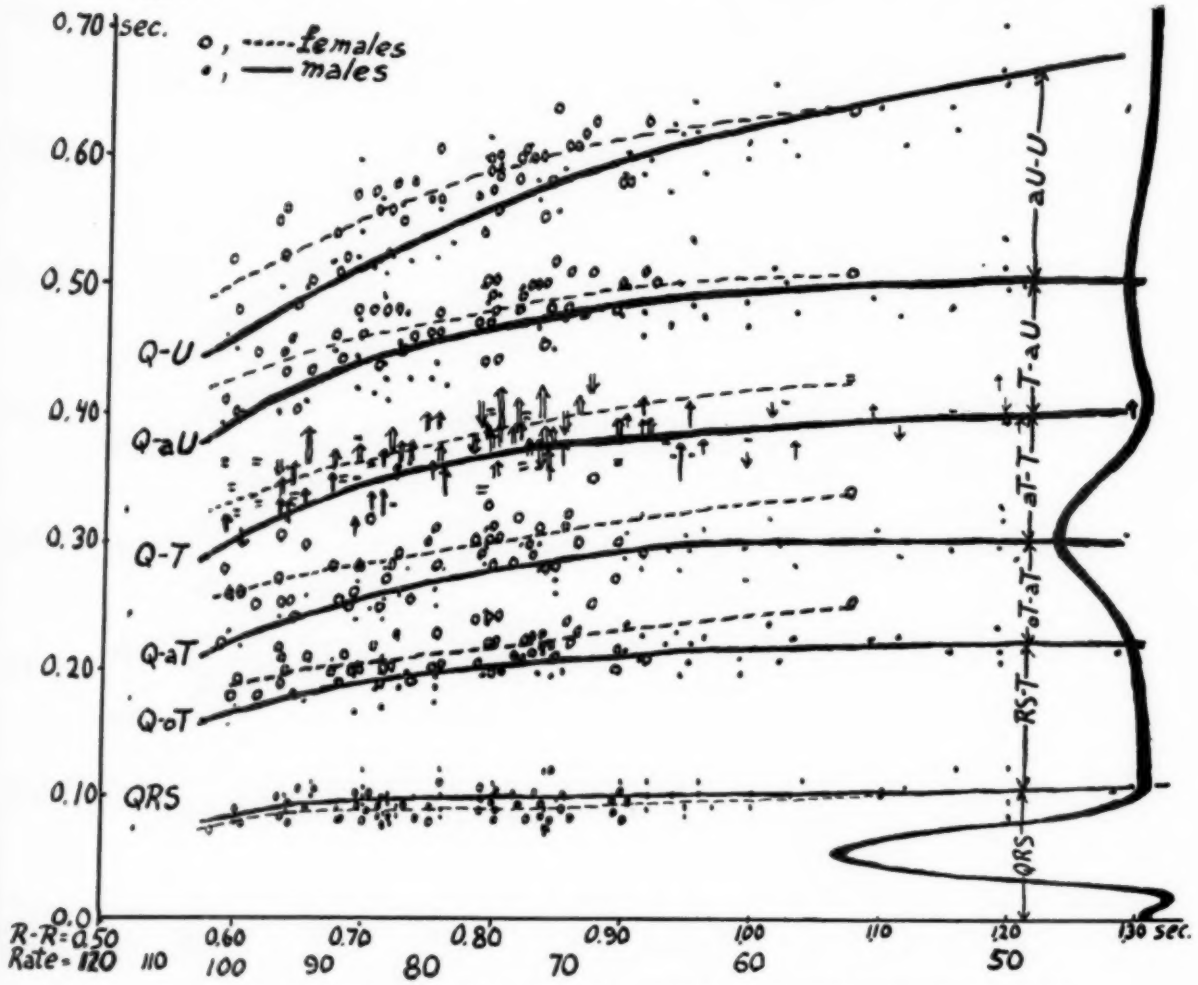

Fig. 2.—The dependence of the intervals of the ventricular electrocardiogram on the heart rate and the interval between two complexes (R-R interval) in 100 normal persons. The dots are single observations while the lines are smoothed averages. In the case of the Q-T interval the end of the T wave is designated by the origin of each arrow, while the beginning of the second heart sound corresponds to the point of the arrow. A horizontal line indicates that both are identical. Double lines represent women; single lines represent men.

The duration of the interval from the beginning of QRS to the origin of the T wave (*Q-oT interval*) ranged from 0.16 to 0.25 second. This duration showed a definite relation to the R-R interval, ranging from 0.16 to 0.21 second for R-R intervals of 0.60 to 0.80 second, and from 0.20 to 0.26 second for intervals exceeding 0.80 second (Fig. 2). Throughout the entire range of heart rates the women showed an approximately 0.015 second longer *Q-oT interval* than the men. As the women showed on the average a shorter QRS duration than the men, the difference in the duration

of the RS-T segment between the sexes is even greater. At an R-R range of 0.60 to 0.92 second, for instance, the average RS-T interval measured 0.100 second for men and 0.120 second for women. This difference was emphasized previously by Ashman.[4]

Because of the pronounced dependence of the *Q-oT interval* on the heart rate, this interval was expressed also as a percentage of the actual Q-T duration and as a percentage of the theoretical Q-T duration expected for the heart rate. This latter percentage appeared useful chiefly under certain conditions when an accurate determination of the actual Q-T duration is impossible because of fusion of the T and U waves or other causes.[5] The *Q-oT interval*, expressed as a percentage of the actual Q-T interval, ranged from 51 per cent to 64 per cent; it showed no apparent relation to the heart rate. The average for women was 57.5 per cent and 56.5 per cent for men. The average age of all women having values above the mean was 42 years, while the average for values below the mean was 39 years; the same averages for men were 33 and 28 years, respectively. The values thus show a tendency to increase with the age, but this tendency is probably not significant.

The duration of the *Q-oT interval*, expressed as a percentage of the expected Q-T interval for the heart rate, ranged from 52 per cent to 70 per cent. The average for women was 63 per cent, while the average for men was 56 per cent. As we shall see later, women in this series showed a corrected Q-T duration on the average 7 per cent longer than the predicted value for the heart rate. If these 7 per cent are added to the predicted value of Q-T in women, the average of Q-oT expressed as a percentage of the predicted Q-T duration becomes 56 per cent and the range 45 to 63 per cent for both men and women.

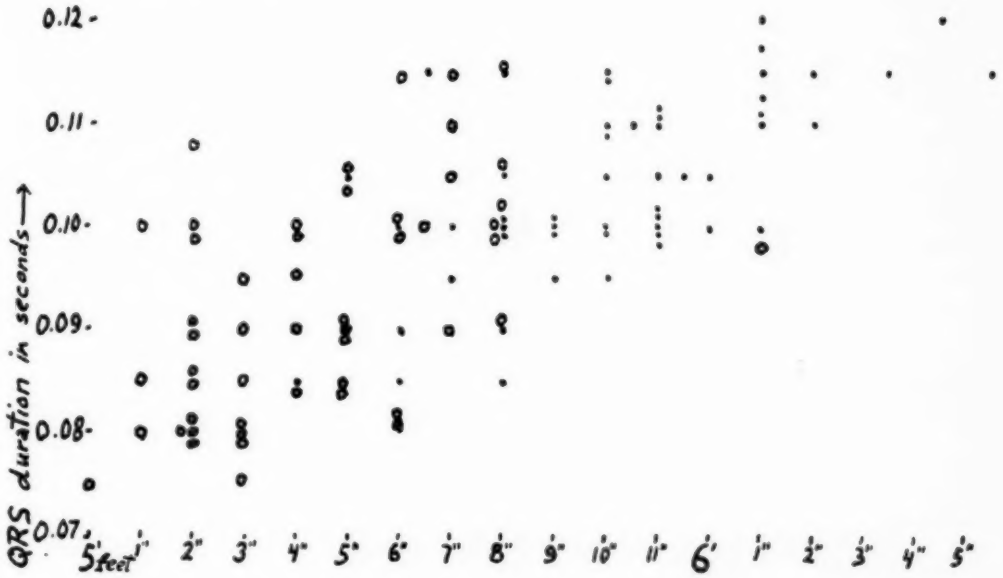

Fig. 3.—Dependence of the QRS interval on the body size in 100 normal persons. Dots represent men while circles represent women.

The duration of the interval from the beginning of QRS to a point one-half the distance of the apex of T from the beginning of QRS (*Q-T/2 interval*) ranged from 0.16 to 0.28 second. It showed the same dependence on the heart rate as the Q-oT interval. In men it was, on the average, 0.005 second longer while in women it was approximately 0.02 second longer than Q-oT. Expressed as a percentage of the actual Q-T duration, it ranged from 52 per cent to 68 per cent. The average for men was 58 per cent, while the average for women was 62 per cent. The average age of all women having values above the mean was 44, while that for values below the mean was 35. The corresponding average ages for men were 34 and 28, respectively. There is, accordingly, a definite

tendency for the values of this interval to increase with age. It is possible that the higher values in women are partly due to the higher average age. However, this factor can play only an insignificant role as the average values were definitely higher in women than in men even in the same age groups. For example, the mean value for the age group 20 to 30 was 61 per cent in women and 57 per cent in men, while the values in the age group 40 to 60 were 62 per cent in women and 58 per cent in men. This study, accordingly, indicates that in men the RS-T segment is farther away from the base line, and the ascent to the apex of T is more even than in women.

The interval from the beginning of QRS to the apex of the T wave (*Q-aT interval*) ranged from 0.22 to 0.35 second. The absolute values of Q-aT showed a definite dependence on the heart rate (Fig. 1). Expressed as a percentage of the actual Q-T duration, its values ranged from 68 to 84 per cent and showed no apparent relation to the heart rate. The mean value for women was 77.5 per cent, while for men it was 76.5 per cent. This difference is very small, whereas the differences in the Q-oT and Q-T/2 intervals were considerable. This indicates that the last section of the ascending branch of the T wave is steeper in women than in men, 22.5 and 23.5 per cent of Q-T, respectively, while the descending branch of T shows no significant differences. The average age of all women having values above the mean was 40, while that of women below the mean was 38. The corresponding values were 31 and 29 for men.

The Q-T duration showed the expected dependence on the R-R interval; at all heart rates the women had a Q-T duration 0.02 to 0.03 second longer than that of the men. Expressed as a percentage of the Q-T duration expected for the heart rate according to an empirical curve based on averages of 5,000 cases,[1] the Q-T duration ranged from −8 to +18 per cent. The mean for women was +8.5 per cent while that for men was +1.5 per cent. Women with values above the mean had an average age of 40, while those with values lower than the mean had an averare age of 39. The corresponding ages for men were 31 and 30, respectively. It is apparent, therefore, that women have on the average a 7 per cent higher and longer Q-T duration than men and that age is not a factor responsible for this difference. Ashman[1,4] found a similar difference amounting to 3 per cent between men and women in 1,000 cases while Shipley and Hallaran[8] found this difference on the average to be 5 per cent in 200 cases. In the group studied by Adams[9] this difference increased from 0.05 per cent at a heart rate of 55 to 6 per cent at a heart rate of 110. However, most formulas for the determination of the Q-T duration corrected for the heart rate currently in use do not take sex into consideration. On the other hand, it is apparent that the curve developed by one of the authors[1] can be applied without correction only to men, while about 5 per cent must be subtracted from values of Q-Tc found when the curve is applied to women.

The onset of the second heart sound occurred from 0.02 second before to 0.03 second after the end of the T wave. The interval T-2d sound (*T-2S interval*) accordingly ranged from −0.02 to +0.03 second. In men the mean value of this interval was zero for a heart rate of 60 and +0.01 second for a heart rate of 100, while in women it was +0.005 for a heart rate of 66 and 0.015 for a heart rate of 100. The *T-2S interval*, accordingly, becomes slightly more positive with rising heart rate. The differences between the sexes are negligible. A similar dependence of the interval on the heart rate also was observed by other authors.[6,7] The age of all women having more positive intervals than the mean was 42, while the age of women having less positive intervals was 38. The corresponding ages for men were 34 and 27. The older persons, thus, seem to have slightly more positive intervals, but the differences are too small to enable any definite conclusion.

The interval from the apex of T to the beginning of the second heart sound ranged from 0.06 to 0.12 second for both sexes. The mean for a heart rate of 100 was 0.082, while for the heart rate of 60 it was 0.092 second. The interval, accordingly, shows a slight increase with a slower heart rate.

The interval from the beginning of QRS to the apex of the U wave (Q-aU interval) ranged from 0.39 to 0.52 second and showed a definite dependence on the heart rate (Fig. 2). As can be seen from the figure, the mean for women was slightly higher than that for men at all heart rates, but especially at high heart rates.

The interval from the beginning of the second heart sound to the apex of the U wave (2S-aU interval) ranged from 0.04 to 0.14 second. The mean value for both men and women was 0.085 second at a heart rate of 100 and 0.10 second at a heart rate of 60. The average age of all women

having values above the mean was 39 while the age of those with values below the mean was 40. The corresponding ages for men were 36 and 26 respectively.

The interval from the end of the T wave to the apex of the U wave (*T-aV interval*) ranged from 0.06 to 0.15 second. The mean at 0.10 second was independent of the sex and showed only a difference of 0.005 second between the high and low heart rates.

The *Q-U interval* showed an even greater dependence on the heart rate than the Q-aU interval (Fig. 2). It ranged from 0.44 to 0.68 second, with the mean value increasing from 0.48 second at a heart rate of 100 to 0.66 second at a heart rate of 60. The interval from the apex to the end of U (aU-U interval) was influenced by the heart rate more than any other interval. It had a mean value of 0.07 second at a heart rate of 100 and 0.14 second at a rate of 60. No differences between the sexes were found.

DISCUSSION

We have mentioned before that one of the most important factors determining the duration of the electrocardiographic intervals is the heart rate. It is of interest to compare the relative dependence of these intervals on the heart rate by determining the percentile increase for each interval as the R-R interval is increased 100 per cent from 0.60 second to 1.20 second. For the duration of the QRS complex this increase amounts to 23 per cent. A similar relation was found by other authors.[1] It can be explained by an increase in the intraventricular conduction velocity by the factors (sympathetic nervous and hormonal action and elevation of body temperature) which are responsible usually for a high heart rate. However, it is impossible to say how much of this dependence is due to the influence of the heart rate proper, as the taller persons tend to have a slower heart rate. In order to answer this question it would be necessary to study the relation to the heart rate within each height bracket, and a much larger material than the present one would be needed. Since the increase of QRS duration from the highest to the lowest heart rate was 23 per cent, while that from the lowest to the highest body size was 44 per cent, it is evident that the body size and, accordingly, the heart size plays a greater role in determining the QRS duration than the heart rate.

The duration of the RS-T segment (measured from the end of QRS to the origin of the T wave) shows a much greater dependence on the heart rate than the QRS duration. Within each sex, it shows an increase of 50 per cent when the R-R interval is increased 100 per cent from 0.60 to 1.20 second. The duration of the ascending branch of the T wave (oT-aT interval), the descending branch of T (aT-T interval), the Q-T/2 interval, the Q-oT interval, and the Q-aT interval all show no dependence on the heart rate when expressed as a percentage of the Q-T interval. All these intervals accordingly show the same dependence on the heart rate as Q-T, increasing 32 per cent when the R-R interval is increased 100 per cent.

The duration of the Q-aU interval increases 28 per cent while the duration of the Q-U interval increases 43 per cent when the R-R interval is increased 100 per cent; the increase is in the first case smaller, in the second larger than that of the Q-T duration. This corresponds to the fact that the interval from the end of the T wave to the apex of U (T-aU interval) shows an increase of only 5 per cent, while the interval from the apex to the end of the U wave (aU-U interval) increases 100 per cent. The total duration of the U wave increases 67 per cent at the same time under the same circumstances.

In contrast to all other intervals of the electrocardiogram, the interval between the end of T and the beginning of the second heart sound shows an inverse relation to the R-R interval; we have mentioned that this interval averaged zero at an R-R interval of 1.20 second and +1.5 second at an R-R interval of 0.60 second. Because of this inverse relation, the interval from the apex of T to the beginning of the second sound (aT-2S interval) shows an increase of only 12 per cent when the R-R interval increases 100 per cent. On the other hand, the interval between the second sound and the apex of the U wave (2S-aU interval) shows a greater dependence on the heart rate than the T-aU interval; the former increases 25 per cent when R-R is doubled. It is of interest that the increase of the interval from the second heart sound to the phase of rapid ventricular filling in the electrokymogram also shows an increase of 25 per cent under the same conditions, while the duration of the rapid filling phase increases 90 per cent—a value approaching that for the descending branch of the U wave. These values were calculated from the figures of Heyer and associates.[10]

The results of this study confirmed the importance of the differences in the duration of the electrocardiographic intervals between the sexes. It was found that the QRS duration was about 6 per cent lower in women than in men at all heart rates. This difference is due exclusively to the smaller body size of the women, as there was no difference between the sexes when the QRS duration was correlated with the body height.

The Q-T duration was about 7 per cent longer in women than in men at all heart rates, and the Q-oT, Q-aT, oT-aT, aT-T intervals showed the same behavior. As the QRS interval was shorter in women than in men, the duration of the RS-T segment showed even greater differences between the two sexes. In addition to these differences in duration, the RS-T segment of the women was less steep than that of the men. The angle between R-ST and T was accordingly much more acute and the origin of the T wave much easier to determine in women than in men. The halfway point of the T wave was situated nearer the apex of T in women than in men. Of all the intervals, the greatest absolute differences in duration between the sexes for a given heart rate were shown by the interval from the end of QRS to the halfway point of T.

No significant differences between the sexes were found in the interval from the end of the T wave to the apex of the U wave (T-aU interval), in the interval from the apex to the end of U (aU-U), and in the relations of the beginning of the second sound to the T and U waves (aT-2S, T-2S and aU-2S intervals). The uniformity of the T-aU and aU-U intervals resulted in the fact that the Q-aU and Q-U intervals showed less pronounced sex differences than the Q-T interval.

A peculiarity in the configuration of the U waves found in a considerable number of women but in none of the men was a diphasic U wave in left precordial leads. In cases showing this pattern the initial section of the U wave had a downward course, forming a distinct kink with the descending branch of the T wave. The U wave then showed a negative nadir followed by a positive summit, which occurred later than the summit of U in leads where this wave was monophasic (usually Lead V_3).

One of the questions which still have to be answered by future studies is whether or not the characteristic differences in the form and duration of the ventricular complex in men and women are due in part to a higher degree of physical fitness and training in athletic activities in the case of the men. It is well known that training increases the vagal tone, and this in turn may cause a shortening of the corrected Q-T duration.[1] In order to answer this question it would be necessary to examine a group of women whose physical activity is completely comparable to that of the average man.

No exact correlation between the age and the duration of the intervals was attempted in this paper, but as an approximate criterion, the average ages of persons having greater than average values, as well as those having lower than average values, were determined. The former were 4 years older in the case of the Q-oT interval, 7.5 years older in the case of the Q-T/2 interval, 2 years older in the case of the Q-aT interval, and only 1 year older in the case of the Q-T interval. The Q-aT and Q-T intervals, accordingly, seem to have no significant dependence on age while the intervals pertaining to the RS-T segment increase slightly with age.

SUMMARY

1. In fifty normal men and fifty normal women the synchronous standard limb and precordial leads as well as the heart sounds were registered at rest. The following intervals were measured: the intervals from the beginning of the QRS complex to the end of this complex (QRS), to the origin of the T wave (Q-oT), to the apex of the T wave (Q-aT) to the end of the T wave (Q-T), to the "halfway point of T" (Q-T/2), to the apex of the U wave (Q-aU), and to the end of the U wave (Q-U). The origin of the T wave or the end of the RS-T segment was defined as the point most distant from a straight line connecting the RS-T junction with the apex of T. The relation of the beginning of the second heart sound to the apex and end of T and to the apex of U was also studied. All values were correlated with the heart rate and the age and sex, and in some cases also with the body height.

2. The QRS duration, when measured from the earliest to the latest points in synchronous leads, is greater than when measured in separate limb leads. It increases slightly with decreasing heart rate but shows the greatest relation to the body size. Men have a greater QRS duration than women, but in the same height groups the values were equal for both sexes. The upper limit for a height up to 5 feet 6 inches was 0.10 second, that for a height from 5 feet 6 inches to 6 feet was 0.11 second, and that for a height from 6 feet to 6 feet 6 inches was 0.12 second. Of nine persons over 6 feet tall, seven had a QRS exceeding 0.11 second.

3. The Q-T duration increases with decreasing heart rate; at all heart rates women had on the average a 7 per cent longer Q-T duration than men. The components of Q-T (Q-oT and Q-aT) showed the same dependence on the heart rate as the entire Q-T interval. When expressed as a percentage of the Q-T interval expected for the heart rate, Q-oT ranged between 49 and 63 per cent, while Q-aT ranged between 62 and 92 per cent, independently of the heart rate and sex. Of

all the components of Q-T, the RS-T segment was the most elastic, showing the greatest differences between the sexes and at high and low heart rates. QRS was the most rigid component.

4. The interval from the end of T to the apex of U was practically independent of the heart rate and sex; it averaged 0.10 second. The Q-aU interval expected for a certain heart rate can be easily determined, therefore, by adding 0.10 second to the Q-T interval expected for this rate. The interval from the apex to the end of U was influenced by the heart rate more than any other interval, but as the determination of the end of U especially at high heart rates was difficult, this observation should be interpreted with caution.

5. The second heart sound began within 0.03 second before or after the end of the T wave, 0.06 to 0.12 after the apex of T and 0.04 to 0.14 second before the apex of the U wave. At lower heart rates it tended to begin up to 0.01 second earlier.

6. The electrocardiogram of women is characterized not only by a longer duration of Q-T and its components Q-oT and Q-aT but also by a longer and more horizontal RS-T segment than that of men. The point when the T wave reaches one-half of its final amplitude is situated nearer to the apex of T in women than in men. These characteristics make it possible, in most normal cases, to distinguish the electrocardiogram of a woman from that of a man.

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THE DIAGNOSIS OF POSTERIOR MYOCARDIAL INFARCTION

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INVESTIGATION of the diagnostic accuracy of the vectorcardiogram, as compared to the electrocardiogram, in myocardial infarction was undertaken in this laboratory. Several striking discrepancies were disclosed, and these will be reported in detail in subsequent communications. The present study was carried out to elucidate some questions raised by these observations, and those aspects of it which are related to the electrocardiographic diagnosis of infarction of the posterior wall of the left ventricle will be discussed in this paper.

Vectorcardiograms have been obtained on over 600 patients. Abnormal initial forces in the QRS loop characteristic of posterior (diaphragmatic) infarction have been recognized in fifty-nine patients; the clinical history was consistent with coronary disease, and the electrocardiograms were confirmatory in all of them. These present no problem. The QRS loops in nine additional patients presented grossly abnormal initial forces of a different kind, suggesting, among other possibilities, absence of the forces which normally originate high on the posterior aspect of the heart. In these, other abnormalities indicative of infarction elsewhere were not noted. The clinical pictures in these cases were characteristic of myocardial infarction, but the electrocardiograms consistently failed to be confirmatory. Extensive exploration of the thorax and esophagus by means of unipolar leads yielded little information of value toward the solution of this problem. The vectorcardiograms in thirty-six additional cases presented abnormalities similar to those just referred to, in addition to the usual signs which are considered diagnostic of infarction in other areas.[1,2]

Altogether, the vectorcardiograms of 104 patients were interpreted as indicating infarction of the posterior wall of the left ventricle. In nine, or 8.6 per cent, infarction appeared to be limited to the posterobasal region of the left ventricle, and in thirty-six, or 34.4 per cent, infarction in this region was associated with infarction of other portions of the left ventricle. A high posterior wall lesion, then, was suspected in forty-five, or 43 per cent, of 104 patients whose vectorcardiograms were thought to be characteristic of posterior wall infarction. The problem was to find other evidence of infarction so situated, since, as stated above, electro-

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cardiographic confirmation was lacking in these cases, and opportunities for postmortem examination had not presented themselves. Solution of this problem was undertaken to provide orientation in our work in vectorcardiography, but the results seemed interesting enough to merit publication.

METHODS AND MATERIALS

The answers to two questions were sought: (1) How often does myocardial infarction occur in the posterobasal region of the left ventricle? and (2) Are lesions so situated ever associated with electrocardiographic signs sufficiently characteristic to be diagnostic? The autopsy protocols and clinical records covering the decade beginning in 1941 were examined, and all cases with posterior wall infarction and adequate electrocardiographic study were selected, a total of eighty-six cases.

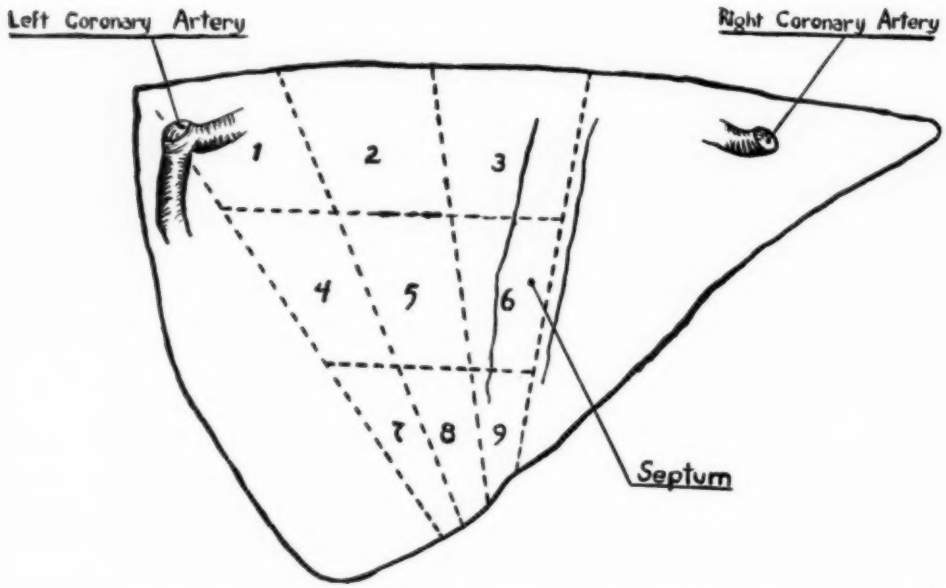

Fig. 1.—Diagram of the unrolled heart. The posterior wall is divided into upper (*1, 2, 3*), middle (*4, 5, 6*), and lower zones (*7, 8, 9*). Posterior infarcts are classified according to areas involved. Involvement of any part or all of the area, *7, 8, 9*, is referred to in the text and figures as *7*.

The following data from the autopsy protocols were tabulated: (1) the precise location on the posterior wall of infarcted areas, (2) the presence or absence of anterior wall infarction, (3) the age of all infarctions, and (4) the heart weight. With few exceptions microscopic sections were available, and these served to confirm the gross appearance and age of the infarctions. The posterior wall of the left ventricle, as seen on the diagram of the unrolled heart,[3] was divided into three horizontal zones: upper or superior, middle, and lower or inferior. Each zone was then divided into three areas: lateral, middle, and septal. As a rule, the lower zone because of its small size was considered as a single area. Thus, the posterior wall was divided into seven (or 9) areas (Fig. 1), and the presence or absence of infarction in each area was noted. In this way the distribution and extent of posterior wall infarcts were clearly depicted, but no estimate of size in

the endocardial to epicardial diameter was made. Anterior infarcts, when present, were classified as acute or old; no estimate of their extent was attempted.

The electrocardiograms were studied without knowledge of the autopsy findings, except for the presence of posterior infarction, and were divided into the following groups in accordance with the interpretation: (1) posterior infarct (Figs. 2 and 3), (2) anterior infarct (Figs. 4 and 5), (3) posterior and anterior infarct (Figs. 6 and 7), (4) abnormal (Figs. 8 to 12), (5) left bundle branch block. The diagnosis of anterior and posterior infarction was made on the basis of the

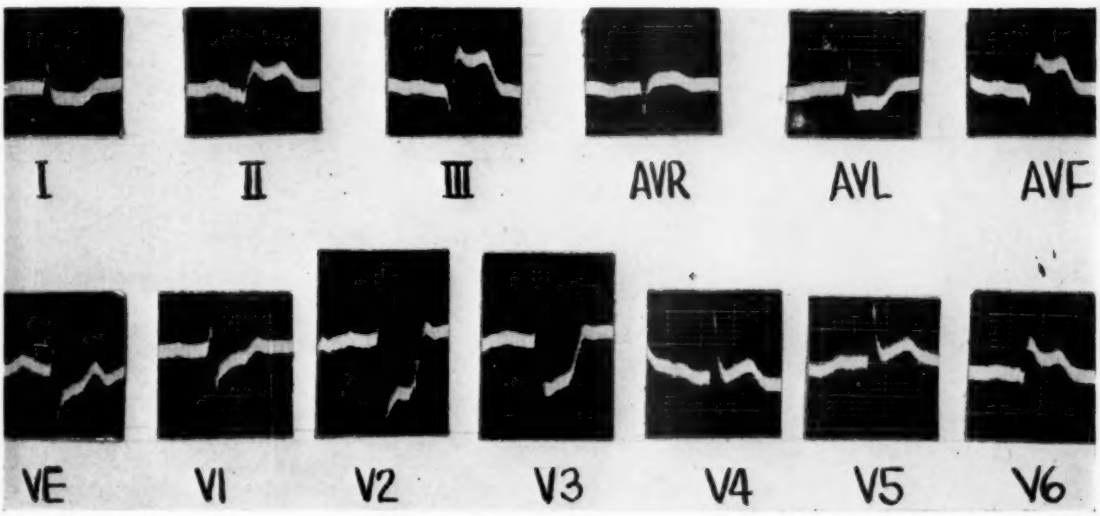

Fig. 2.—Acute posterolateral myocardial infarction. Autopsy revealed acute posterior and anterior myocardial infarction. Areas *4*, *5*, *6* and *7* were involved.

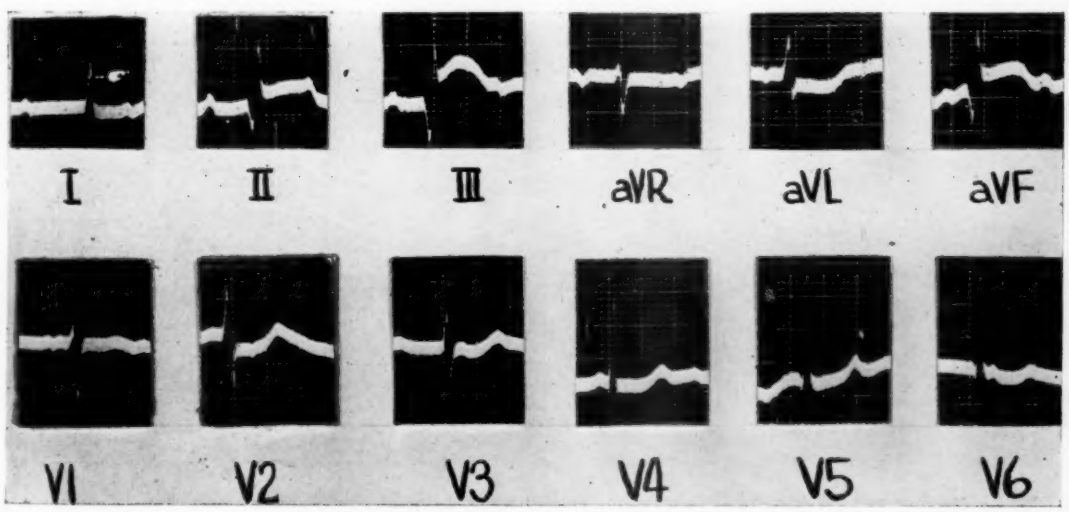

Fig. 3.—Acute posterior myocardial infarction, complete auriculoventricular block. Autopsy revealed acute posterior infarction in areas *3*, *5*, *6*, and *7*.

generally accepted criteria; no distinction was made between acute and old infarction.[4,5] Electrocardiograms were designated as abnormal when the ventricular complex (QRST) presented some deviation from normal of a nonspecific or nondiagnostic nature; abnormalities in rhythm were disregarded.

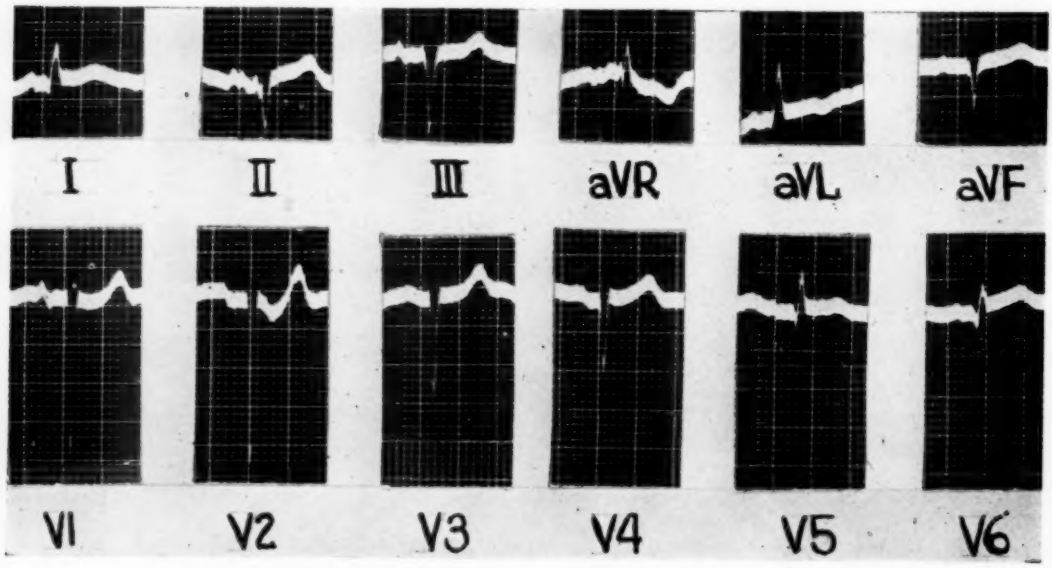

Fig. 4.—Electrocardiogram interpreted as anterior myocardial infarction on basis of QS deflections in V_4 and prominent Q deflections and upward displacement of S-T segments in V_5 and V_6, and Leads I and aV_L. The small initial positive deflections in Leads III, aV_F, and V_1 to V_3, were considered to be against the diagnosis of posterior infarction. However, histologic examination revealed acute infarction limited to areas *2*, *4*, and *5* high on the posterolateral aspect of the free wall of the left ventricle. A few additional leads would have suggested correct localization.

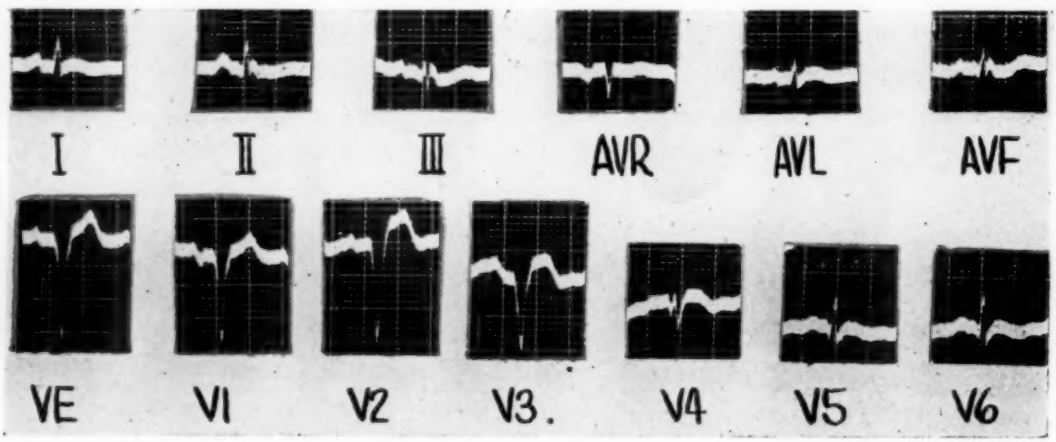

Fig. 5.—Extensive acute anterior myocardial infarction. A diagnosis of acute posterior infarction was not made, the S-T segment depressions in Leads II, III, and aV_F being considered reciprocal to the acute anterior infarction. The small Q waves in aV_F were not considered significant. Histologic examination disclosed acute infarction of the anterior wall and of the posterior wall comprising areas *1* to *7*.

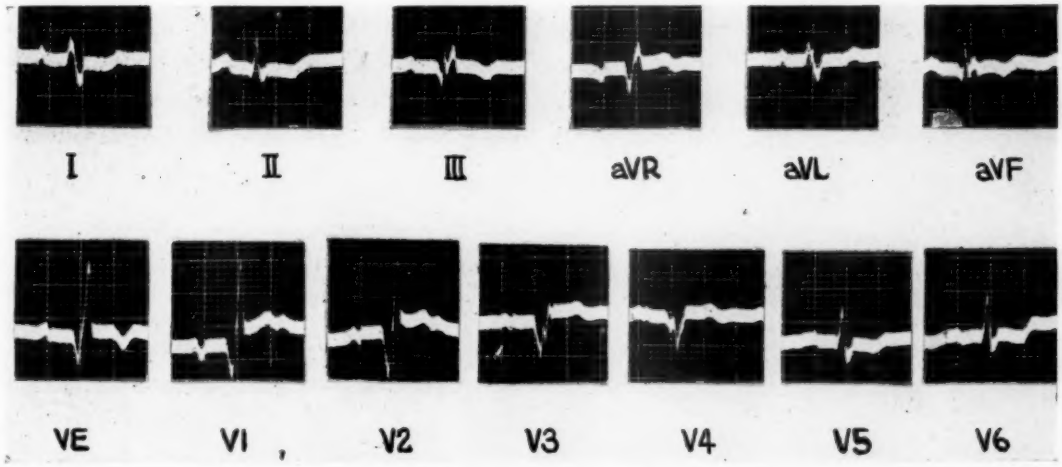

Fig. 6.—Characteristic electrocardiographic signs of acute posterior and acute anterior myocardial infarction, and right bundle branch block. The upward displacement of the S-T segments and the upright T waves in the right-sided precordial leads are indicative of an acute process in the anterior wall; the absence of reciprocal signs in Leads III and aV_F suggest an acute posterior lesion as well. Histologic examination revealed acute posterior and anterior wall lesions, as well as an old posterior infarct. The posterior infarct was acute in area *7*, and old in areas *1*, *2*, and *3*.

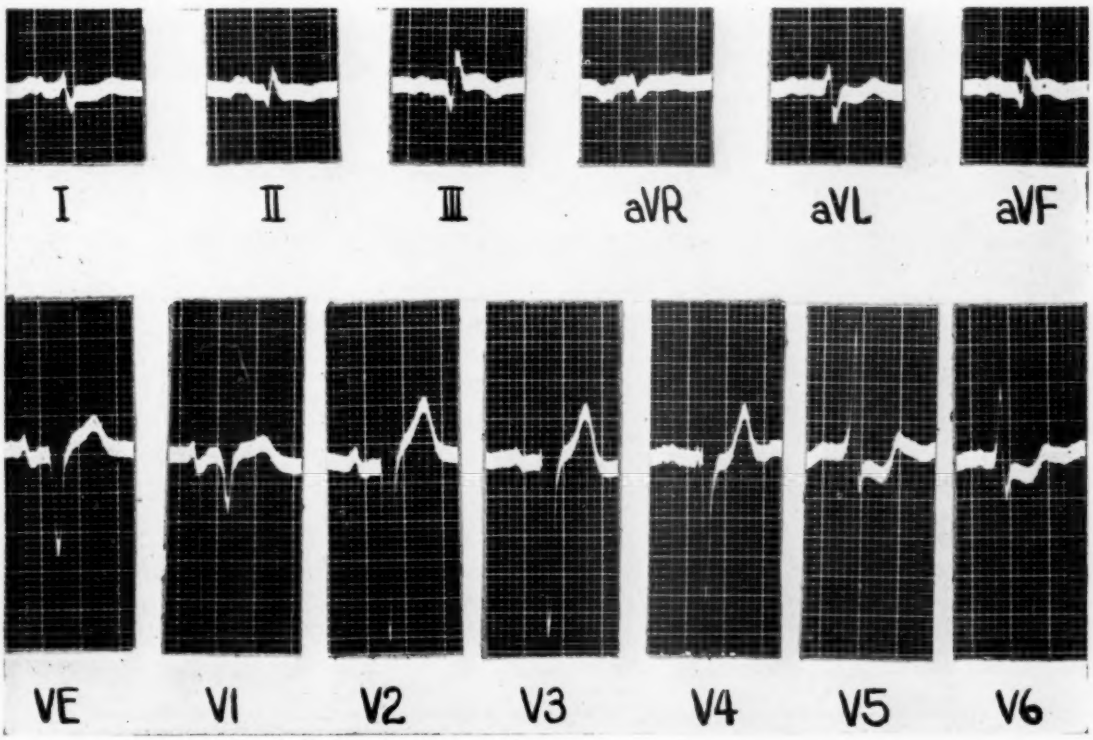

Fig. 7.—Characteristic electrocardiographic signs of acute posterior and acute anteroseptal myocardial infarction in the presence of normal intraventricular conduction. If the QS deflections in the right-sided precordial leads were the result of the posterior infarct, Q waves would be present in Leads V_5 and V_6. Autopsy showed extensive acute anterior and posterior infarction, the latter involving areas *1* to *7*.

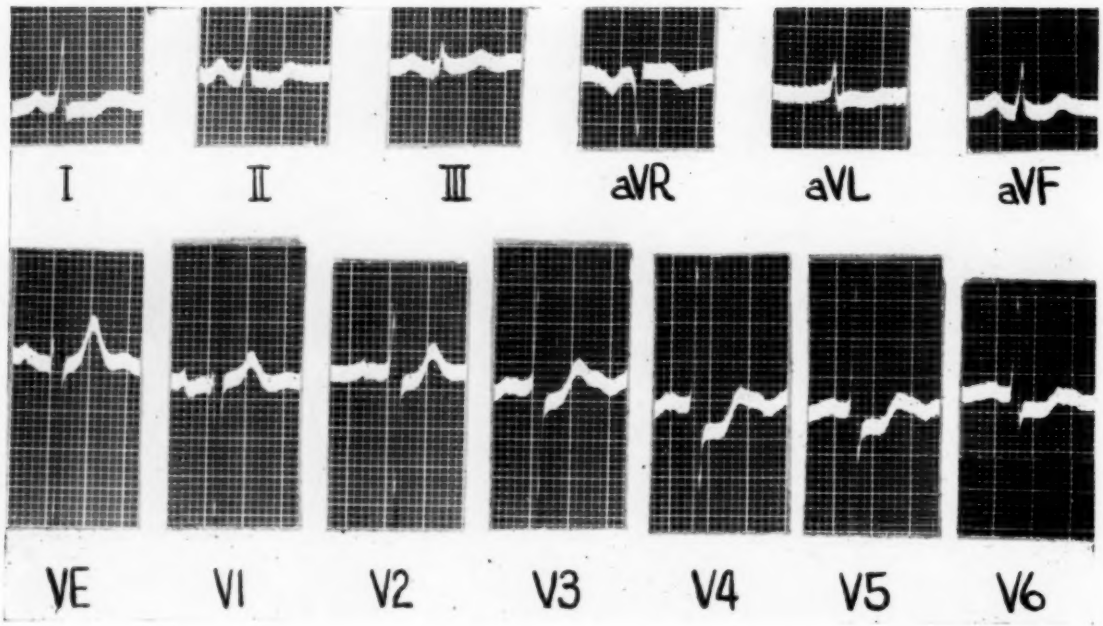

Fig. 8.—Abnormal electrocardiogram. The S-T segment depression in Leads I, II, aV_L, and V_2 to V_6, and the upward displacement of the S-T segments in Lead aV_R, suggest many possibilities, among them acute infarction variously situated. The QRS complex is within normal limits, and the difficulty cannot be resolved. The patient died before another tracing was obtained. Autopsy revealed acute anterior and posterior myocardial infarction, the latter comprising areas *2*, *3*, *4*, *5*, and *6*.

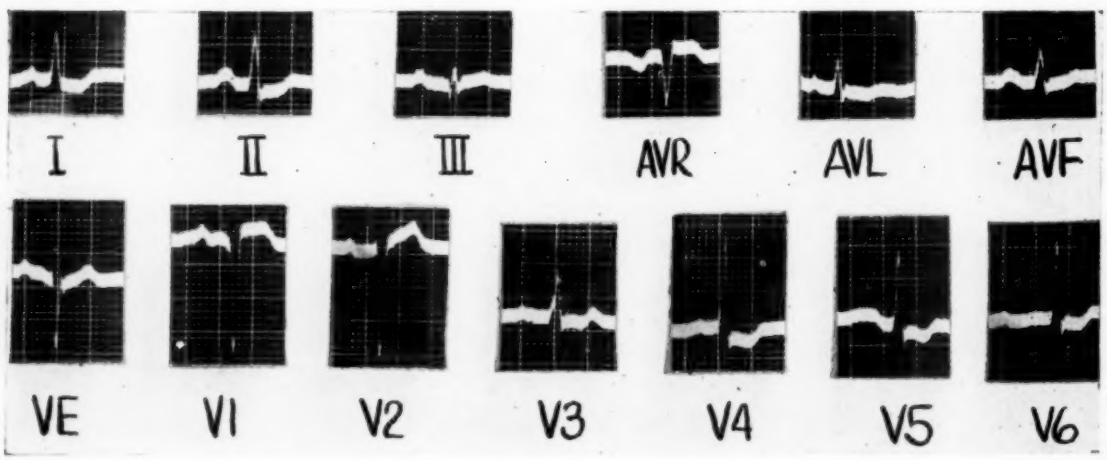

Fig. 9.—Abnormal electrocardiogram. A diagnosis of infarction was not made, although an acute anteroseptal, or a subendocardial infarct could not be excluded. Digitalis was not responsible for the S-T segment deviation. Autopsy showed extensive acute anterior and posterior myocardial infarction, the posterior lesions involving areas *1* to *7*. The difficulty in interpretation may have been due to the presence of two acute infarcts, but this type of tracing, in the light of our studies in vectorcardiography, would now be considered strongly suggestive of incomplete left bundle branch block.

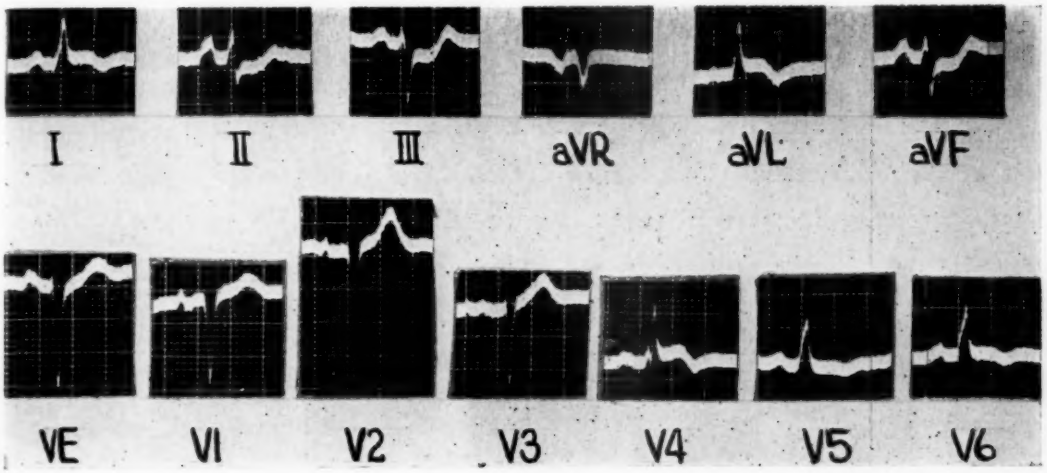

Fig. 10.—Abnormal electrocardiogram. Upward displacement of S-T segments in Leads I, aV_L, V_4, V_5, and V_6, and the downward displacement in Leads II, III, aV_F, and V_E, are characteristic of an "injury pattern" arising in the anterior wall of the left ventricle. There are no QRS changes indicative of infarction, but incomplete left bundle branch block cannot be excluded. Autopsy showed acute anterior and posterior infarction, the latter involving areas *1*, *4*, *5*, *6*, and *7*.

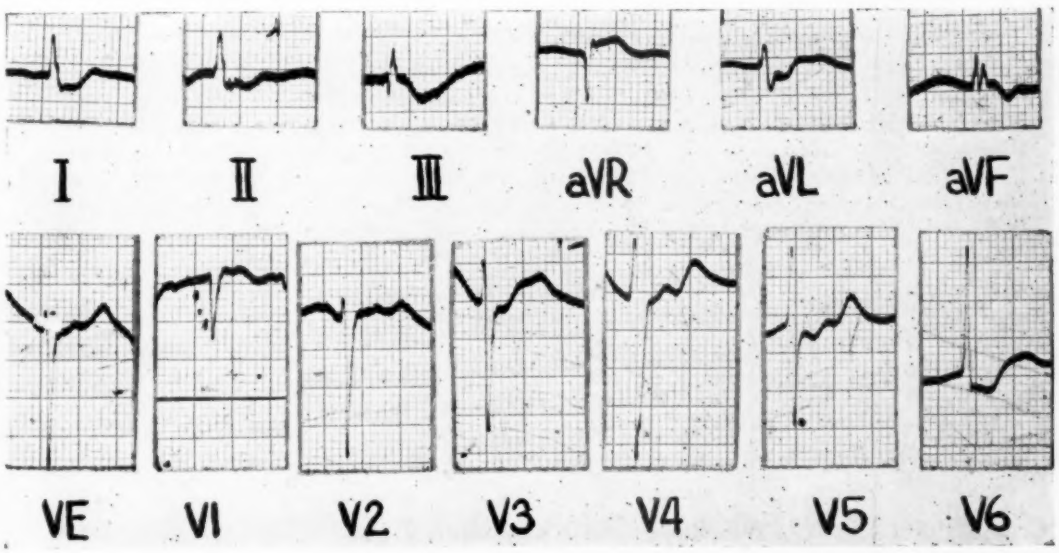

Fig. 11.—Abnormal electrocardiogram. The only abnormalities, in addition to auricular fibrillation, are in the S-T segments and T waves and are of a kind generally considered diagnostic of subendocardial infarction. A diagnosis of posterior infarction was not made because of the absence of Q or QS deflections in Lead aV_F. Histologic examination revealed the presence of an acute posterior myocardial infarction involving areas *2*, *3*, *5*, *6*, and *7*. There was no infarction in the anterior wall.

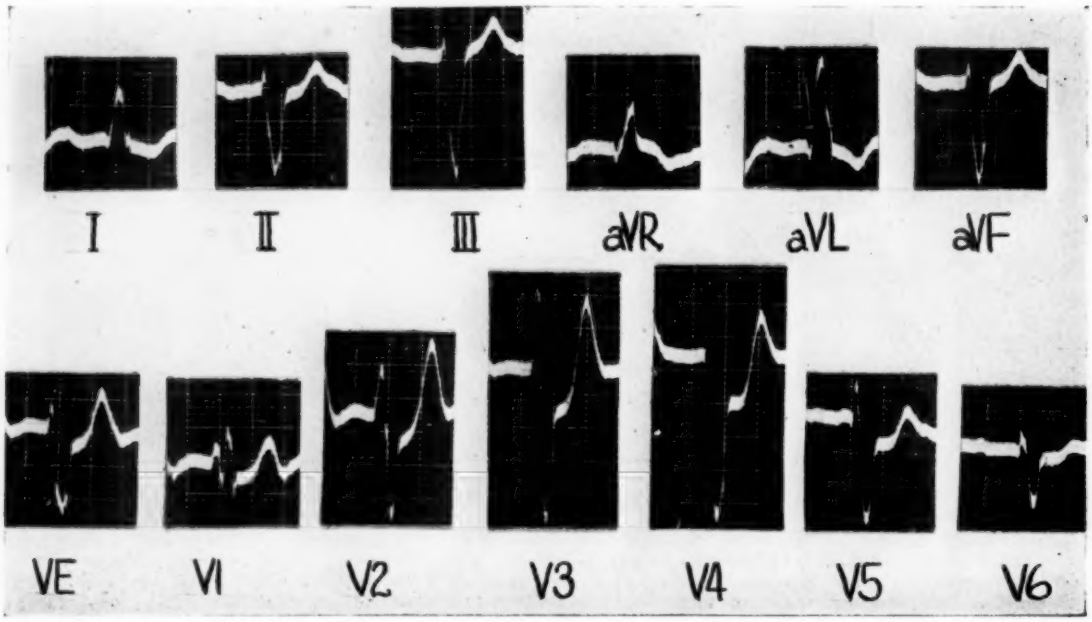

Fig. 12.—According to conventional interpretation a diagnosis of posterior infarction would not be made, and for the purposes of this paper the tracing was classified as abnormal electrocardiogram with intraventricular block. Tracings of this sort are now interpreted in this laboratory as left bundle branch block, septal, and posterolateral myocardial infarction.[18] Histologic examination revealed acute infarction involving the interventricular septum, and the posterolateral wall of the left ventricle, comprising areas *3*, *5*, *6*, and *7*.

The electrocardiograms in six cases consistently displayed left bundle branch block, and these were set aside leaving eighty cases for detailed analysis.*

Localization of Posterior Infarcts.—The detailed localization of infarction in the nine areas of the posterior wall revealed that the lesion was limited to a single area in only one case, to two areas in seven, to three areas in seven, and involved more than three areas in sixty-five patients. Distribution of infarction in the upper, middle, and lower zones (Fig. 1) is shown in Table I. Infarction was limited to a single zone in only eight cases, or 10 per cent of the series, and all three zones were involved in thirty-seven cases, or 46 per cent. The upper two zones combined were infarcted as frequently as the lower two zones (18 per cent).

TABLE I. ELECTROCARDIOGRAPHIC INTERPRETATION AND LOCALIZATION OF POSTERIOR WALL INFARCTION

ECG. DIAGNOSIS	NO. OF CASES	UPPER ZONE	MIDDLE ZONE	LOWER ZONE	UPPER 2 ZONES	LOWER 2 ZONES	ALL 3 ZONES	UPPER AND LOWER ZONES
Post. infarct	33	0	2	2	8	4	16	1
Ant. & Post. infarct	14	0	0	0	2	2	7	3
Ant. infarct	14	0	1	0	3	6	3	1
Abnormal ECG	19	2	1	0	2	2	11	1
Total (%)	80	2 (2.5)	4 (5.0)	2 (2.5)	15 (18.8)	14 (17.5)	37 (46)	6 (7.5)

*There was an additional case of left bundle branch block, classified in this paper as "abnormal." See Legend of Fig. 12.

TABLE II. DIAGNOSIS OF POSTERIOR INFARCTION IN PATIENTS WITH ACUTE, HEALED, AND NO ANTERIOR INFARCTION

AUTOPSY FINDINGS IN 80 PATIENTS WITH POSTERIOR INFARCTION	DIAGNOSIS OF POSTERIOR INFARCTION		
	YES	NO	DIAGNOSED (%)
Acute Anterior Infarct	24	21	53.3
Old Anterior Infarct	10	4	71.0
No Anterior Infarct	13	8	62.0
No or Old Anterior Infarct	23	12	65.0

Anterior wall infarction was noted histologically in fifty-nine cases and was acute in forty-five (Table II). In not a single instance was infarction limited to the lateral wall of the left ventricle.

Electrocardiographic Interpretation.—A diagnosis of posterior infarction was made in thirty-three cases, anterior and posterior infarction in fourteen, anterior infarction in fourteen, and abnormal electrocardiogram in nineteen cases. The diagnosis of posterior infarction, therefore, was made in forty-seven cases, or 58.8 per cent, and was missed in thirty-three. When divided into acute and old lesions, 58.1 per cent of the acute and 61 per cent of the old, posterior infarcts were recognized clinically (Table III). The diagnosis in the missed cases was anterior infarction in fourteen, and "abnormal electrocardiogram" in nineteen cases. In not a single instance was the electrocardiogram interpreted as normal.

Anterior wall infarction, as noted previously, was present in fifty-nine cases and was acute in forty-five (Table II). Ante-mortem diagnosis of anterior infarction was made in twenty-eight cases, in only one of which was it impossible to demonstrate the lesion at autopsy (Fig. 4). The posterior wall lesion was recognized clinically in twenty-four patients, or 53 per cent of the forty-five cases with proved acute anterior infarction, and in ten, or 71 per cent of fourteen cases with proved healed anterior infarction. An electrocardiographic diagnosis of posterior infarction was made in thirteen, or 62 per cent of the twenty-one cases in which there was no anatomical evidence of an anterior wall lesion (Table II). The diagnosis of posterior infarction in relation to various combinations of acute and old posterior and anterior lesions is shown in Table III.

TABLE III. DIAGNOSIS OF POSTERIOR INFARCTION IN VARIOUS COMBINATIONS OF ACUTE AND OLD ANTERIOR AND POSTERIOR INFARCTION

AUTOPSY FINDINGS	NO. CASES	DIAGNOSIS OF POSTERIOR INFARCTION		
		YES	NO	DIAGNOSED (%)
All cases	80	47	33	58.8
Acute posterior infarction (All cases)	62	36	26	58.1
Old posterior infarction (All cases)	18	11	7	61.0
Posterior infarction alone	21	13	8	62.0
Acute	16	11	5	68.7
Old	5	2	3	40.0
Acute posterior infarction plus anterior infarction (Acute Anterior 41) (Old Anterior 5)	46	25	21	54.0
Old posterior infarction plus anterior infarction (Acute anterior 4) (Old anterior 9)	13	9	4	69.2

The diagnosis of posterior infarction was missed in the two cases in which the lesion was limited to the upper zone; the infarct was acute in one case, old in the other; there was no infarction of the anterior wall in either case. The correct diagnosis was made in the two cases in which the lesion was confined to the lower zone; both infarcts were acute, and the anterior wall was normal. In four cases infarction was limited to the middle zone. The correct diagnosis was made in two of these one an acute, the other an old infarct; both had old anterior wall infarct. In the third case, autopsy showed old posterior and anterior infarcts, but only the anterior infarct was recognized in the electrocardiogram. In the fourth case, the electrocardiographic interpretation was "abnormal," and autopsy disclosed an acute posterior infarct involving two areas of the middle zone; there was no anterior wall infarction.

It may be seen from Table I that posterior infarction was diagnosed ante mortem in ten of the fifteen cases in which the lesion was confined to the upper two-thirds of the posterior wall, and in six of the fourteen cases in which the lower two-thirds of the posterior wall was involved. At autopsy eight of the ten correctly diagnosed cases of the former group displayed acute posterior infarction and in three of them acute anterior infarction was also present. Among the five cases that were undiagnosed during life all had acute posterior infarction and four of them had acute anterior infarction in addition. Post-mortem examination in the fourteen cases with infarction of the lower two-thirds of the posterior wall disclosed that four of the six cases in which the diagnosis of posterior infarction was made during life had acute posterior and anterior infarction. Among the eight cases in which posterior infarction was missed there were six with acute posterior infarction, and, of these, five also had acute anterior infarction; acute anterior infarction was present in a sixth case, one with an old posterior infarct.

Posterior infarction was recognized ante mortem in twenty-three of the thirty-seven cases in which all three zones were infarcted and was missed in fourteen. In the diagnosed cases the posterior infarct was acute in eighteen, in thirteen of which acute anterior infarction was disclosed at autopsy. Among the fourteen undiagnosed cases the posterior infarct was acute in eleven, and an acute anterior infarct was demonstrated post mortem in nine of them.

Heart Weight.—The relationship between heart weight and the reliability of the electrocardiogram in the diagnosis of posterior myocardial infarction is shown in Table IV. The correct diagnosis was made in seventeen, or 60.7 per cent of the twenty-eight cases in which the heart weight was less than 400 grams, and in thirty, or 57.7 per cent of fifty-two cases in which the heart weight was 400 grams or more. When the cases are divided into groups with and without acute anterior

TABLE IV. RELATION OF HEART WEIGHT TO THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF POSTERIOR INFARCTION

AUTOPSY DIAGNOSIS IN 80 CASES OF POSTERIOR INFARCTION	NO. OF CASES	POSTERIOR INFARCT DIAGNOSED BY ELECTROCARDIOGRAM		
		ALL CASES	HEART WEIGHT UNDER 400 GRAMS	HEART WEIGHT 400 GRAMS OR MORE
Acute anterior infarction	45	24 (53%)	10 out of 16 cases (62.5%)*	14 out of 29 cases (48%)*
No or healed anterior infarction	35	23 (65%)	7 out of 12 cases (58%)	16 out of 23 cases (69.5%)
All cases	80	47 (58.8%)	17 out of 28 cases (60.7%)	30 out of 52 cases (57.7%)

*Statistically not significant. See text.

infarction, it is seen (Table IV) that in the latter group an electrocardiographic diagnosis of posterior infarction was made in 58 per cent of the cases in which the heart weight was less than 400 grams and in 69.5 per cent when the heart weight was 400 grams or more. In the cases with acute anterior infarction diagnosis of the posterior lesion was made in 62.5 per cent of the cases with heart weights under 400 grams and in 48 per cent in those with heart weights over 400 grams.

DISCUSSION

Isolated, high posterior infarcts are not included in the diagnostic classification of electrocardiographers[4,5] but were presumed to exist when abnormal vectorcardiograms of a peculiar kind were observed.[1,6] Although an isolated lesion confined to the upper zone was demonstrated in only two cases in the autopsy series, they, nevertheless, provide the sought-for anatomico-pathologic basis for the high posterior infarcts diagnosed by vectorcardiography. There is, however, a discrepancy between the incidence of histologically proved lesions limited to the upper zone and the number of vectorcardiographic diagnoses of posterobasal infarct, 2.5 per cent of eighty cases of posterior infarction in the former and 8.6 per cent of 104 cases of posterior infarction in the latter. Perhaps better agreement should not be expected, since it might be anticipated that the incidence of small isolated lesions would be greater in a group of patients who survived an attack of myocardial infarction than in a group of patients who succumbed. It is possible that isolated lesions in the middle zone should be included in this category, and if the four cases so qualified are added to the two in the upper zone, there are six cases of high posterior infarcts, an incidence of 7.5 per cent which is in close agreement with the 8.6 per cent observed by vectorcardiography. But until there is available considerable anatomic evidence in cases which have been studied by vectorcardiography, the correlation between the histologic location of posterior infarcts and what we now presume to be the vectorcardiographic signs of high posterior infarction will be unknown.

These data suggest that the vectorcardiogram has a wider range of usefulness than the electrocardiogram in the diagnosis of posterior infarction and that a significant number of all posterior infarcts remain undiagnosed by electrocardiography because of position of the lesion. Furthermore, incomplete electrocardiographic diagnosis occurs in an even larger number of cases, since both the autopsy series and the vectorcardiographic series clearly indicate that high posterior lesions occur much more commonly in association with infarct elsewhere than as isolated lesions. Although diagnostic electrocardiographic signs of infarction occur in some of these cases, the existence of high posterior infarction is not revealed; therefore, the true extent of infarction is not appreciated. It may be mentioned here that there was not a single instance of anatomically proved isolated high lateral wall infarction and that such a diagnosis was not made in any of the cases of infarction studied by vectorcardiography. Although it may be impossible to demonstrate more than a lateral wall infarct by electrocardiogram, vectorcardiographic studies indicate, and autopsy findings prove, that such infarcts usually extend laterally from the high posterior wall and sometimes from the anterior wall in addition.

It is well known that the "electrocardiographic signs characteristic of infarction are not a'ways observed when the clinical picture obviously indicates this diagnosis." Such failure occurs "when the infarct is small, when it is entirely intramural, i.e., does not reach the endocardial or epicardial surfaces, when it is unfavorably situated in regard to the leads obtained, and when left bundle branch block is present."[7] Nevertheless, failure to make a diagnosis of posterior infarction in thirty-three out of eighty cases, which compares favorably with published figures,[8-12] is a challenge to the electrocardiographer. Smallness of the lesion did not account for many failures in this series, since infarction was limited to a single area in only one case and involved more than three areas in sixty-five of the eighty cases. High position of the infarct, however, was a more common cause of failure, especially if we are correct in including middle zone lesions in this category; thus, only two of the six high infarcts were diagnosed ante mortem. Of the four cases that were missed, two had old infarcts involving one and two areas, respectively, and two had acute infarcts, each involving two areas; none of them were associated with acute anterior infarction.

The generally known fact that acute infarcts, because of their characteristic and rapidly changing S-T segments and T waves, are diagnosed more often than are old infarcts, is borne out in this study. However, this is not evident when the entire series of eighty cases is divided into two groups, one with acute and the other with old, posterior infarcts, without reference to other factors. As a matter of fact, it appears that posterior infarcts are diagnosed more readily when old than when acute (Table III). It became apparent, in looking for an explanation for this unexpected result, that acute anterior infarction plays an important role in concealing the electrocardiographic signs of posterior infarction (Tables II and III). This is shown by the prevalence of old, in contrast to acute, anterior infarcts in the group with old posterior infarction (Table III). The over-all effect of acute anterior infarction on the diagnostic value of the electrocardiograms in cases of posterior infarction is demonstrated by the statistical treatment of the data for the entire series (Table II).* The Chi square test with one degree freedom showed that there was a significant difference (Chi square = 5.23) between the per cent of posterior infarcts correctly diagnosed in the group with acute anterior infarcts compared to the group without acute anterior infarct. The influence of acute anterior infarction in masking the electrocardiographic signs of posterior infarction was also revealed in a study of septal infarction previously reported from this laboratory.[13] It was shown that the number of cases in which the simultaneous existence of acute anterior and posterior infarcts was proved histologically greatly exceeded the number in which the combined lesions had been recognized electrocardiographically. This means that acute infarction in one area may conceal the electrocardiographic evidence of associated infarction in another area. The effect of acute anterior infarction in preventing the development of the diagnostic electrocardiographic signs of posterior infarction contrasts with the well-known lack of such influence in the case of healed anterior infarct.[14]

*The statistical analyses were made by Marvin Schneiderman, Biometric Section, National Cancer Institute, Bethesda 14, Md.

It has been thought by some that left ventricular hypertrophy conceals the electrocardiographic signs of infarction.[12] In view of the common association of chamber enlargement and coronary heart disease this factor, if true, would be of great importance. Since fifty-two of the eighty cases had hearts weighing 400 grams or more, and fifty-nine had anterior infarcts (forty-five of them acute), it was considered necessary to form separate groups, i.e., with and without acute anterior infarction, in order to estimate what influence, if any, hypertrophy had on the electrocardiographic pattern of infarction. When this was done it became evident that hypertrophy played no part in concealing the electrocardiographic features of posterior infarction (Table IV). The Chi square test with one degree of freedom showed that there was no significant difference between the per cent correctly diagnosed in the group with acute anterior infarcts for hearts weighing below 400 grams compared with those weighing more than 400 grams.

The lack of relationship between heart weight and the electrocardiographic diagnosis of posterior infarction is shown also in Fig. 13, in which heart weights are plotted against per cent of positive diagnoses.

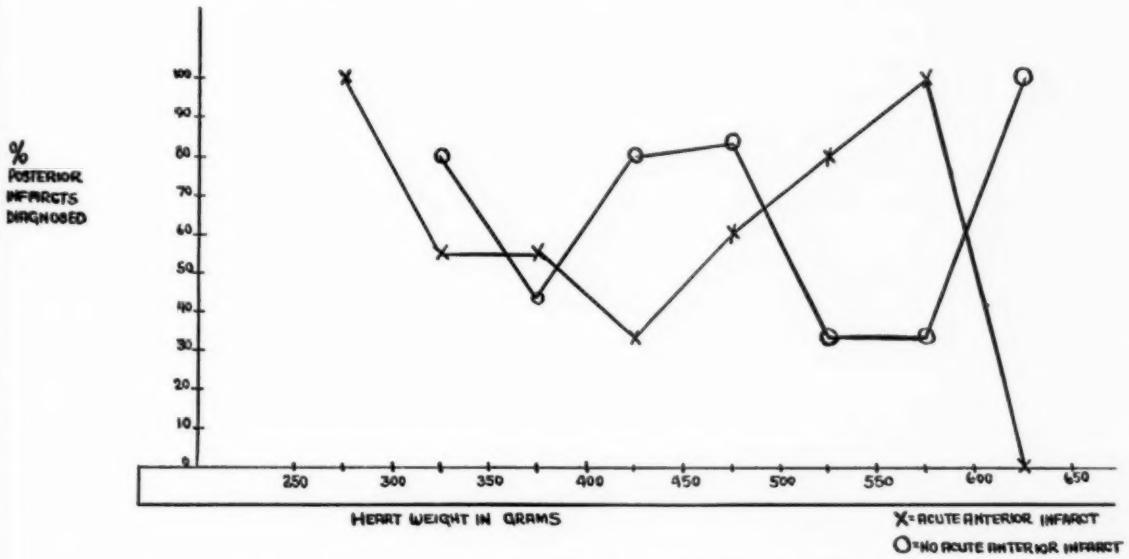

Fig. 13.—Per cent positive diagnoses of posterior infarcts plotted against heart weight.

THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF INFARCTION

The electrocardiographic diagnosis of infarction is made possible because the direction, and to a lesser extent, the magnitude of the initial and/or early manifest resultant vectors are changed in a characteristic manner when forces normally present disappear as a result of the myocardial lesion.[15] Since altered heart position and rotation of the heart may affect the initial vectors in a similar manner, it is understandable that infarction may be simulated when none is present. On the other hand, anomalous conduction[7,16] and defective intraventricular conduction of certain types may prevent the characteristic changes from occurring, so that

the signs of infarction are concealed, though a lesion exists. Also, small infarcts may not alter significantly the direction of the initial vectors, or the changes secondary to lesions in certain locations may not be evident in the planes which are represented by the leads obtained. Finally, when multiple infarcts occur, the forces which are thereby eliminated may have had diametrically opposite directions; consequently the new instantaneous resultant vectors, though reduced in magnitude, may be normal in direction or not altered sufficiently to be diagnostically significant. In either event, the development of the characteristic signs of infarction is prevented.

It is not surprising, then, that the electrocardiogram, in some cases, fails to reveal the presence of myocardial infarction despite the existence of such a lesion, but it is somewhat disconcerting that failure occurs in such a large proportion of the cases. It may be instructive, therefore, to review the failures in an attempt to expose the mechanism involved.

The diagnosis was missed in eight of the twenty-one cases in which posterior infarction was the sole lesion. The high position, small size, and age of the infarcts were possible causes in six cases. In another case an acute posterolateral infarct was mistaken for an anterolateral lesion, an error which might have been avoided by obtaining a few additional exploratory leads (Fig. 4). There was a large acute infarct in the eighth case, and this is the only one in this group in which there is no apparent explanation for diagnostic failure.

The remaining twenty-five cases in which the posterior infarct was not recognized ante mortem had anterior wall lesions in addition to the posterior ones. In twenty-one of these, the anterior infarction was acute and possibly interfered with the development of the signs of posterior infarction. Furthermore, in three of these the posterior lesions were old. The anterior infarct was old in four cases and cannot be considered a significant factor in the diagnostic failure. In one of these cases there was an old posterior infarct confined to two areas, and in another the area of old and acute infarction was confined to the basal region of the posterior wall. There remain only two cases in which the mechanism responsible for diagnostic failure is entirely obscure.

There is, then, an explanation in thirty-six of the thirty-nine cases in which the electrocardiogram failed to reveal the presence of posterior wall infarction. We have reason to believe that incomplete left bundle branch block, which effectively conceals the evidence of infarction, is much more common than current electrocardiographic diagnosis indicates. This conduction disturbance is often difficult to recognize but should always be considered when myocardial infarction is strongly suspected but not shown in the tracings (Figs. 9 and 10). This is a possibility in the three cases in which the cause of diagnostic failure remained obscure. This question is of more than academic interest, since it is possible to abolish left bundle branch block by simple measures in some cases.[17] If this can be accomplished in a substantial number of cases a notable improvement in the diagnostic value of the electrocardiogram will have been achieved. Diagnostic accuracy will be further increased if a diagnosis of posterior infarction is considered when tracings which clearly reveal the presence of acute anterior infarction

do not display reciprocal changes, or when the latter are poorly developed. It is a reasonable assumption that posterior infarction is also present when tracings which show an acute anterior infarct suddenly display bundle branch block or high grade auriculoventricular block.[13] Finally, S-T segment depression, or tall R and T waves in the right-sided precordial leads, may represent the reciprocal and sole changes occurring as the result of high posterior infarction (Figs. 8, 9, 11). These tracings often are erroneously interpreted as indicating a subendocardial lesion. Despite these possible improvements, our preliminary experience with vectorcardiography suggests its superiority over electrocardiography in relation to the diagnosis of posterior myocardial infarction.[6]

SUMMARY

An anatomico-pathologic basis for the vectorcardiographic diagnosis of high posterior infarct has been demonstrated. Autopsy findings and vectorcardiographic diagnosis indicate that almost one tenth of all infarcts involving the posterior wall of the left ventricle are small and are limited to its upper portion. Even more common are infarcts so situated but extending to other portions of the left ventricle. The importance of these observations lies in the fact that the high posterior infarcts do not, as a rule, produce diagnostic signs in the electrocardiogram. Consequently, many posterior wall infarcts are overlooked, and in an even larger number of cases the extent of the lesion is minimized.

Our preliminary studies in vectorcardiography have directly or indirectly confirmed some generally accepted explanations for the diagnostic failure of the electrocardiogram in cases of infarct and have revealed some new ones. The observations herein reported demonstrate some of the limitations of the electrocardiogram in relation to the diagnosis of posterior infarction. Diagnostic failure is witnessed when the electrocardiogram discloses left bundle branch block, when the posterior infarct is small, located high on the posterior wall, is old, or is associated with acute anterior wall infarction. Old anterior wall infarction and left ventricular hypertrophy do not interfere with the development of the electrocardiographic signs of posterior infarction.

It is noteworthy that not a single electrocardiogram in this series of cases was interpreted as normal. An abnormal electrocardiogram, then, obtained in a patient with a clinical picture of acute coronary heart disease, should be considered consistent with, but not diagnostic of, acute infarction. The electrocardiogram was interpreted as abnormal in nineteen of the eighty cases, and in twelve of them anterior infarction was also present. Since acute anterior infarction commonly conceals the electrocardiographic signs of posterior infarct, the latter should be suspected in some cases in which the electrocardiogram shows only acute anterior infarction, especially when changes reciprocal to the anterior infarct are poorly developed or absent and when bundle branch block or high-grade auriculoventricular block appears during the course of the illness. The electrocardiographic changes in high posterior infarct may consist solely of S-T segment depression or tall R and T waves in the precordial leads.

CONCLUSIONS

1. Eighty-six unselected cases with proved (autopsy) posterior wall infarction and satisfactory electrocardiographic observations were studied. The purpose of this investigation was to ascertain if, and how often, localized high posterior wall infarction occurred, since preliminary vectorcardiographic studies suggested such lesions in 8.6 per cent of all patients with posterior wall infarction. It was desired also to ascertain whether or not the electrocardiogram was ever of diagnostic value in these cases.

2. The electrocardiograms in six cases consistently displayed left bundle branch block. These were set aside, leaving eighty cases for detailed analysis and study.

3. Isolated high posterior wall lesions were found in six, or 7.5 per cent of the eighty unselected cases with proved posterior wall infarction. These constitute the indirect anatomico-pathologic evidence for the high posterior infarcts diagnosed by vectorcardiography in 8.6 per cent of 104 cases with posterior wall infarction. The two infarcts limited to the upper zone, and two of the four limited to the middle zone, were not recognized by electrocardiography, indicating a very limited value of the electrocardiogram in the diagnosis of high posterior lesions.

4. Posterior infarction was correctly diagnosed by electrocardiography in forty-seven, or 58.8 per cent of the eighty cases. The electrocardiographic diagnoses were: (a) posterior infarction, 33 cases; (b) anterior and posterior infarction, 14 cases; (c) anterior infarction, 14 cases; and (d) abnormal electrocardiogram, 19 cases. Anterior infarcts were demonstrated histologically in all but one of the cases in which this diagnosis was made ante mortem. Not a single electrocardiogram was interpreted as normal.

5. Posterior infarction was not diagnosed by electrocardiogram in thirty-nine of the eighty-six cases with proved posterior wall lesions. The factors responsible for failure were evident in thirty-six cases, as follows (only single items are given, although multiple causes were operative in some cases; old posterior infarct was commonly combined with other factors): (a) left bundle branch block, 6 cases; (b) acute anterior infarction, 21 cases; (c) localized, high infarcts, 7 cases; (d) old, small infarct, 1 case; (e) inadequate electrocardiographic exploration, 1 case; and (f) unknown, 3 cases.

6. Old anterior infarction and left ventricular hypertrophy do not diminish the diagnostic value of the electrocardiogram in posterior infarction.

7. Methods of improving the diagnostic value of the electrocardiogram for posterior infarction are discussed.

8. The vectorcardiogram appears to be superior to the electrocardiogram for the diagnosis of posterior myocardial infarction.

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THE VENTRICULAR ESOPHAGEAL ELECTROCARDIOGRAM IN THE DIAGNOSIS OF MYOCARDIAL INFARCTION

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AFTER Wolferth and Wood[1] published their first clinical paper on the use of the precordial leads in the study of the anterior surface of the heart, Lieberson and Liberson[2] revived the esophageal lead technique "to portray more inimately the electrical phenomena at the posterior surface and the base of the heart."

Waller[3] first used the alimentary route in the human being by placing an electrode in the mouth. In 1906, Cremer[4] passed an electrode down the esophagus of a professional sword swallower with radiographic aid. He advocated wider use of the method because it permitted the closest approach to the heart. Many investigators[5-7] have utilized the anoesophageal lead in experimental animals.

Lieberson and Liberson in their use of the esophageal lead were most impressed with the high auricular complex which closely resembled that obtained by the direct auricular lead of Sir Thomas Lewis. Therefore, it was used chiefly as an adjunct in the analysis of auricular electrical activity in the diagnosis of the arrhythmias.[8-10]

Brown[8] demonstrated that the esophageal lead pattern in dogs resembled closely the tracing obtained from a direct lead applied to the underlying posterior wall of the heart. He was the first to show the possibilities of this lead's clinical significance. However, it was Hamilton and Nyboer[11] who focused the attention of the medical profession on the use of the esophageal lead in the study of myocardial infarction. They showed that the precordial electrocardiograms characteristic of anterior myocardial infarction resembled the esophageal tracings which were characteristic of posterior myocardial infarction. Nyboer[12] later presented a case of posterior myocardial infarction in which (seventeen years after the acute episode) the standard leads were equivocal but the esophageal leads were diagnostic. A few years later, Nyboer[13] studied ten cases of posterior myocardial infarction in which the esophageal lead was diagnostic, whereas in several of the cases the standard leads were doubtful. His criteria for a significant Q wave in the esophageal lead for the diagnosis of posterior myocardial infarction were "a Q wave which is 0.04 mv. or deeper, 1/5 or more of the R wave, when the esophageal lead is 5 cm. or more below the auricle as judged by the P wave."

Myers and Oren[14] studied twenty-five cases in which a diagnosis of posterior myocardial infarction had been made by means of serial tracings, esophageal leads, or autopsy evidence. With

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the use of the esophageal lead they established a diagnosis of previous posterior myocardial infarction in twenty-one of twenty-five cases, and excluded such infarction in twenty-two of twenty-five control cases. In all the control cases a prominent Q_3 or QS_3 was present. There was a prominent Q_3 and an absent QaV_F in two cases in which the esophageal lead revealed an infarct located high on the posterior wall, close to the auricular margin. They suggested as esophageal lead criteria in the diagnosis of posterior myocardial infarction that the Q wave should have a depth of 0.04 mv. or more, or be at least 25 per cent of the R wave.

Burchell[15] found, in a series of fifty cases, that the esophageal electrocardiograms which might be regarded as diagnostic of posterior myocardial infarction are usually associated with a suggestive or diagnostic Q_2, Q_3 pattern in the standard leads. He implied that where a Q_3 is the only abnormal finding, the esophageal lead is frequently equivocal.

Because of the technical difficulties involved, the esophageal lead has never become popular in the diagnosis of posterior myocardial infarction. The unipolar extremity potential of the left leg, Lead aV_F, as introduced by Wilson[20,21] and augmented by Goldberger[22] has been widely employed, therefore, in attempting to make this diagnosis. The Q wave in Lead aV_F is usually considered significant if it is 25 per cent or more of the R wave and if it is 0.04 seconds or greater in duration. The esophageal electrocardiogram at the ventricular level closely approximates the configuration of Lead aV_F in the majority of cases.[19] Helm, Helm, and Wolferth[16] believe that there is little advantage in utilizing the diaphragmatic pattern in the esophagus in addition to the left leg extremity potential. However, Burchell[15] points out that in some patients with right bundle branch block associated with a posterior myocardial infarction, the esophageal lead often gives useful confirmatory evidence. Myers and Oren[14] and Nyboer[13] found excellent agreement between the significant Q waves in Lead aV_F and in the esophageal lead at the ventricular level.

Myers and associates[18] reported four cases of posterior myocardial infarction confirmed at autopsy which had abnormal Q waves in the esophageal lead. In one case, the Q-R ratio was within normal limits but the R wave was coarsely notched on the upstroke. At autopsy the lesion was found to involve the subendocardial one-half of the entire posterior wall.

Two of the authors[17] from a series of cases having a Q wave in Lead III believe that the best electrocardiographic evidence of posterior myocardial infarction is the presence of a deep Q wave in the esophageal lead at the ventricular level. They conclude that the esophageal lead and Lead aV_F approximate each other with greater accuracy than standard Lead III in evaluating the diagnosis of posterior myocardial infarction.

Sandberg and associates,[24] from a recent study, state that although the finding of a deep Q wave 25 per cent or more of the R wave at the ventricular level without an abnormal Q in Lead V_F may indicate a localized posterior infarction, such patterns may also be seen in normal individuals.

Evans and Black[25] in a study of ten patients with pneumoperitoneum without evidence of heart disease found abnormally large Q waves associated with abnormal T waves in the esophageal leads at the ventricular level in 100 per cent of the cases. Because the heart was displaced forward and upward in each case they felt that this was probably the most important factor in the production of these abnormal Q waves.

Scherlis and associates[27] feel that the left leg lead reflects the potentials of the diaphragmatic surface of the ventricle as accurately as does the esophageal lead.

Bain[28] studied the esophageal lead in cases of posterior myocardial infarction and in none was any information obtained from the esophageal lead that was not present in Lead V_F. In high posterior infarcts the area of damage was too close to the transitional zone to make the signs of infarction reliable.

The esophageal and other leads were studied by Oram and associates[29] in posterior myocardial infarction. They concluded that in view of the slight superiority of Lead V_F over the gastroesophageal leads and the disadvantage of the latter, such as unpleasantness to the patient, the frequent occurrence of artifacts, the close resemblance between the normal transitional zone and the pathological ventricular level tracings, and the fact that the electrode at times may be in juxtaposition to the right ventricle instead of the left ventricle, there would appear to be no case for the employment of the esophageal leads in the diagnosis of posterior cardiac infarction.

The literature is somewhat conflicting regarding the value of the esophageal leads in the diagnosis of posterior myocardial infarction. In an attempt to further clarify this problem, we have studied the esophageal leads in one hundred patients with Q waves in standard Lead III and/or abnormal T waves in Leads III and aV_F.

METHOD

In this study the Nyboer electrode was used. It consists of a thin rubber tube with metal bands fixed at regular intervals, each of which is connected by means of a separate wire to a master switch. To this switch, the exploring electrode wire was attached. Multiple leads were thus taken without moving the tube. A Goldberger central terminal was used as the indifferent electrode.

Our earlier studies were done with a string electrocardiograph. Because of the many technical difficulties encountered, a direct-writing electrocardiograph was later used. The advantages in the use of this machine were more accurate standardization, decreased motion of the base line, and the ability to see the tracing as it was recorded.

The esophageal lead was passed through the nares. If there was nasopharyngeal obstruction, the oral route was employed. There was little difficulty encountered in passing this tube; occasionally a 1 per cent Pontocaine spray to the pharynx facilitated its passage. The tube was usually passed to 70 cm. The position of the tube was always noted since swallowing or retching by the patient could appreciably change the position.

The criteria used for the diagnosis of myocardial infarction were a definite history, corroborative clinical and laboratory findings, and/or unequivocal electrocardiographic changes. The diagnosis of posterior myocardial infarction was based upon the findings of a Q wave in Lead aV_F with an amplitude of 25 per cent or more of the R wave in this lead. The significance of the Q wave was considered to be enhanced when its duration was 0.04 seconds or more and when it was followed by an inverted T wave. The criteria used for significant Q waves in the esophageal lead at the ventricular level were identical with those used for aV_F. Patients who did not satisfy the above criteria were not considered to have posterior myocardial infarction. Patients were classified as borderline when the findings were of possible significance but were equivocal.

MATERIAL

One hundred patients were selected who were in the hospital for various conditions including cardiac disease. The cases were chosen because of the presence of a Q wave in either Lead III or Lead aV_F, or abnormal T-wave changes in both of these leads. No cases receiving digitalis were selected on the basis of T-wave changes alone. In each case, the standard leads, three or more precordial (CF_1 or V) leads, the augmented unipolar extremity leads, and the esophageal leads were taken. These leads were correlated with the previous electrocardiograms, the clinical history of the patient, and the available post-mortem findings.

RESULTS

1. Cases with Posterior Myocardial Infarction.—There were sixty-four patients who were considered to have evidence of posterior myocardial infarction. In five of these cases post-mortem examination was performed. The findings are discussed subsequently. In forty-five cases, the Q in both aV_F and EV was 25 per cent or more of the corresponding R wave (see Fig. 1).

In six cases there was not a deep Q wave in aV_F or in EV. One case had a deep Q_3. The diagnosis of posterior myocardial infarction in these patients was based upon the presence of inverted T waves in Leads III, aV_F, and EV in the absence of digitalis therapy or an enlarged left ventricle. All of these patients had histories suggestive of myocardial infarction or the anginal syndrome.

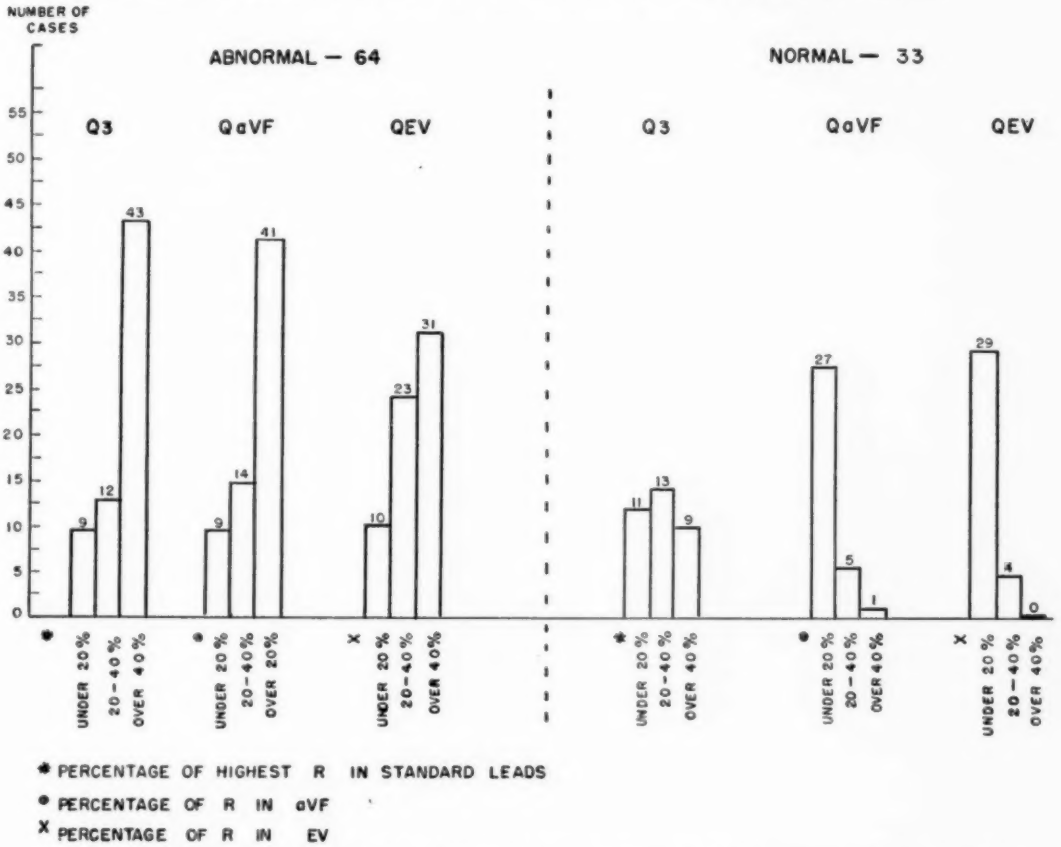

Fig. 1.—Distribution of depth of Q_3, QaV_F, and QEV in 64 cases with and 33 cases without posterior wall infarction.

In eight patients there was a small Q wave in the esophageal leads at ventricular levels associated with a deep Q wave in Lead III and aV_F. The T wave in aV_F was negative in seven and the T wave in EV was negative in five. Two of these patients had anterior as well as posterior myocardial infarction.

Five patients had a small Q in Lead aV_F associated with a deep Q in EV. Only one patient had an associated deep Q_3. Three of these patients had small R waves in Lead III. The T wave in Lead aV_F was negative in all three cases. The T wave in EV was negative in three and diphasic in one.

Thirty-nine patients had diphasic or negative T waves in EV; (see Fig. 3) nine of these had neither diphasic nor negative T waves in aV_F. Twelve had a negative T in aV_F and neither a diphasic nor an inverted T in EV. Thirteen had normal T waves in both the esophageal leads and lead aV_F. One patient had elevated S-T segments in EV and aV_F; however, a myocardial infarction had occurred seven days prior to the examination.

The Q waves in the esophageal leads at ventricular levels were 0.02 seconds or less in duration in twelve cases (see Fig. 2). Three of these Q waves were 25 per cent or more of the R wave in lead EV. The Q in the esophageal leads was 0.04 second or greater in twenty-nine patients. In thirty-one patients the Q wave in Lead EV was less than 3 mm. in depth; fourteen of these were not considered deep in proportion to the R waves in Lead EV.

The Q wave in aV_F was 0.02 second or less in only ten patients; in one of these there was a deep Q aV_F (see Fig. 2).

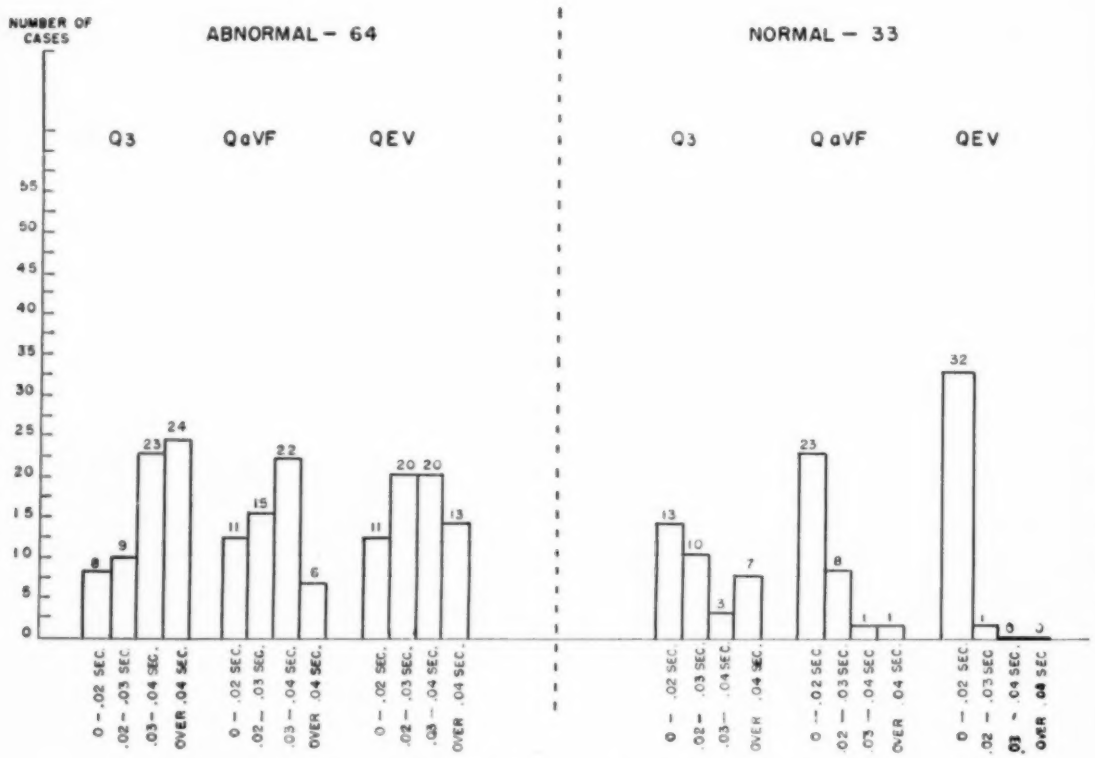

Fig. 2.—Distribution of width of Q_3, QaV_F, and QEV in 64 cases with and 33 cases without posterior wall infarction.

2. Cases without Posterior Myocardial Infarction.—There were thirty-three patients without evidence of posterior myocardial infarction. In three of these post-mortem examinations were performed. In eighteen of these cases, the Q wave in Lead III was 25 per cent or greater than the highest R wave in the standard leads (see Fig. 1).

In five cases, the Q wave in Lead aV_F was 25 per cent or more of R aV_F (see Fig. 1). One patient had a QS wave in aV_F. In three cases the Q wave in aV_F was only 0.02 second long. The fifth patient had a Q wave in aV_F that was 33 per cent of the R wave in aV_F; the Q wave was 0.03 second in duration. This patient had a cyanotic congenital heart disease.

In two patients the Q in aV_F was 0.04 second or longer; one of these had a QS in aV_F. All other patients had a Q wave of less than 0.04 second in Lead aV_F (see Fig. 2). The T wave in aV_F was isoelectric in two patients and was diphasic in one patient who was receiving digitalis and had an enlarged left ventricle. All other patients without posterior myocardial infarction had upright T waves in Lead aV_F (see Fig. 3).

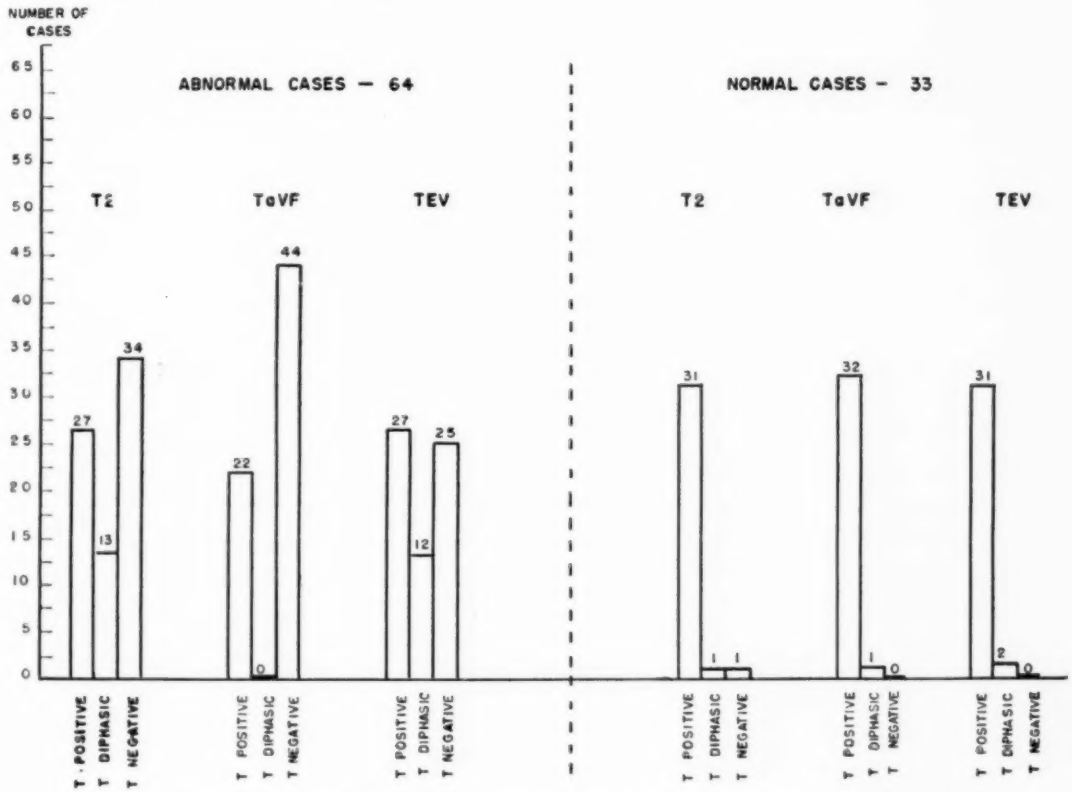

Fig. 3.—Distribution of positive, diphasic, and negative deflection of T waves in Leads II, aV_F, and EV in 64 cases with and 33 cases without posterior wall infarction.

In none of the thirty-three patients was the Q wave at ventricular levels of the esophageal leads (EV) greater than 25 per cent of R EV (see Fig. 1). In none of these patients was the Q wave in EV 0.03 second or greater (see Fig. 2). In none was the Q wave in EV 4 mm. or more in depth; in only one was it 3 mm. deep. None of the thirty-three had a negative T wave in EV (see Fig. 3). Two cases had diphasic T waves in EV; the electrocardiogram of one of these showed the pattern of left ventricular strain.

3. Borderline Cases.—There were three patients in whom no conclusion could be reached regarding the state of the posterior myocardium.

In one there was a deep Q aV_F in proportion to R aV_F (25 per cent, 2.03 seconds in duration) but the QRS of Lead aV_F was low in voltage. No abnormal Q wave was present in EV and the T waves were normal in aV_F and EV. There was a history suggestive of myocardial infarction. However, Lead I showed a diphasic T wave and Lead aV_L an inverted T. These changes may represent an old lateral wall infarction.

One patient had an incomplete right bundle branch block. There was a deep Q aV_F, 33 per cent of R, without a deep Q EV. There was low voltage in aV_F with low negative T waves in Leads aV_F and EV. This patient gave no history suggestive of cardiac disease.

There was one case with a history suggestive of myocardial infarction. There was a deep Q in aV_F, 75 per cent of R aV_F, but the voltage of the QRS complex in Lead aV_F was very low. The Q waves were normal in the esophageal leads, and the T waves were normal throughout.

4. Post-mortem Findings.—In nine cases post-mortem examinations were performed within a short time of the electrocardiographic studies. In three, no posterior myocardial infarction was noted at autopsy; in each of these cases the electrocardiograms were within normal limits. There were small Q waves in Leads III, aV_F and EV in two cases, but these were not of significant amplitude. In one case the Q wave in Lead III was 40 per cent of the highest R in the standard leads. The Q aV_F was 25 per cent of R aV_F, but was only 0.02 second in duration. The Q EV was only 17 per cent of the R EV. The patient had a right bundle branch block.

In six patients posterior myocardial infarction was found at autopsy.

In patient No. 1 the heart showed infarction of the lower and posterior portion of the left ventricle and the adjacent part of the septum. In the electrocardiogram there was a deep Q in Leads III, aV_F and EV, all 0.04 second in duration.

The heart in patient No. 2 weighed 500 grams; the right ventricle measured 3 mm. in thickness, the left, 22 mm. There was a large area of scarring in the posterior wall of the left ventricle; there were marked fibrotic changes in the remainder of the wall of the left ventricle and the septum. The electrocardiogram revealed deep Q waves in Leads III, aV_F and EV with negative T waves in aV_F and EV. There were negative T waves in V_{4-6}; and S-T segments were depressed in Leads I and II. The patient had been receiving digitalis.

Post-mortem examination in patient No. 3 disclosed extensive scleroderma. There was thick fibrous tissue between the visceral and parietal pericardium. The valves were normal. The right ventricle was 4.5 mm. thick, the left 20 mm. thick. The anterior descending branch of the left coronary artery had a pinpoint eccentric lumen with a thickened atheromatous wall. The proximal three centimeters of the circumflex branch of the right coronary artery were almost occluded by intraluminal calcific deposits. There was severe diffuse fibrosis most marked on the posterior surface of the heart, but also involving the entire left ventricle and the septum. The electrocardiogram revealed deep and broad

Q waves in Leads III, aV_F, and EV. The T waves were inverted in Leads II, III, aV_F, $V_{1,2,3}$ and diphasic in V_4.

The heart in patient No. 4 showed a 3 cm. area of infarction of the posterior wall of the left ventricle. There were deep Q waves in Leads III, aV_F, EV, V_6 and V_7; the T wave was diphasic in V_5 and flat in V_6. In addition there was right bundle branch block.

Patient No. 5 had a large anterior wall infarction with aneurysm formation. There was also infarction of the posterior wall. In the electrocardiograms there were deep Q waves in Leads III and Ev with a QS in aV_F. There were deep Q waves with elevated S-T segments in V_{3-6} with negative T waves in V_5 and V_6.

In these five cases there was excellent correlation between the post-mortem findings of posterior wall infarction and the changes in the electrocardiogram in Leads III, aV_F, and EV. Some had associated anterior wall infarction which was also well correlated with the electrocardiogram.

In patient No. 6 the esophageal lead did not reveal any evidence of posterior wall infarction, though Leads III and aV_F were significantly abnormal. The heart showed marked scarring of the anterolateral and posterior walls of the myocardium. There was occlusion of all the major coronary vessels. There was a deep Q_3 and a QS in aV_F. There was only a small Q wave (5 per cent of the R wave) and a normal T in EV. A QS in V_{1-3}, a small Q in V_{4-6} with negative T waves in V_{4-6} reflected the anterior wall infarction.

COMMENTS

Q waves greater than 25 per cent of the corresponding R wave at ventricular levels in the esophageal leads were not found in any of the group without posterior myocardial infarction. None of the patients had a Q EV 0.03 second or greater. Only one had a Q EV of 3 mm. or more in depth. The T waves were upright in all cases except two in which they were diphasic. In five patients the esophageal lead was useful in interpreting the significance of equivocal aV_F leads. The esophageal leads were normal in these patients and compatible with the clinical history.

In extreme degrees of rotation of the heart, as seen in cases with marked elevation of the diaphragm, deep Q waves may occur in the esophageal leads at levels usually considered to be ventricular.[25] With upward rotation of the apex on the transverse axis, there is corresponding lowering of the posterior basal surface of the heart. The auricular and transitional zones are oriented to the lower esophagus, leading to deep Q waves in EV.[26]

A false positive Q wave was not found in the esophageal lead in any of the patients in our series. Sandberg and associates[24] have reported the presence of false positive Q waves in the esophageal leads of normal individuals. A possible reason for this discrepancy is that in our study the ventricular level was determined by the intrinsic P wave and not by the number of centimeters the electrode was from the nares. A lead was not considered to be at the ventricular level un-

less it was more than 7.5 cm. below the level of the last intrinsic P wave, no matter how small the amplitude of the P wave. We are in agreement with Nyboer[23] that this is the only reliable means of finding the ventricular level.

In the patients with posterior myocardial infarction, there were thirteen cases in which there was a lack of correlation between the Q waves in Leads aV_F and EV. In eight cases (12 per cent) there were abnormal Q waves in aV_F and normal Q waves in EV; in only three of these were the T waves in EV also normal. Five patients (7 per cent) had a small Q wave in aV_F associated with a deep Q in EV; only two of these had normal T waves in aV_F. This lack of correlation may be due to the fact that the infarcted area with respect to the esophagus and the left leg may be significantly different. This discrepancy has been discussed at length in a previous report.[17]

On the basis of this study, the esophageal lead at ventricular levels can be considered to indicate the presence of posterior myocardial infarction when the Q wave is 25 per cent or more of the R wave in the same lead. Confirmatory but not necessarily essential criteria are the depth of Q EV to 4 mm. or greater, and the duration of Q EV to 0.04 second or more. A Q EV of 3 mm. in amplitude and between 0.03 and 0.04 second in duration is of possible significance. A negative T wave in the esophageal leads at ventricular levels is probably indicative of posterior myocardial infarction when there is a left ventricular pattern in the absence of such factors as digitalis, hypertrophy of either ventricle, intraventricular conduction defects, and other causes of nonspecific T-wave changes. This appears to be especially true if the T waves are also abnormal in Leads aV_F and III. In six patients in this series, posterior myocardial infarction was present with only T-wave changes in Leads III, aV_F, and EV.

The esophageal leads at ventricular levels were occasionally, though rarely, more valuable than Leads III or aV_F in the diagnosis of posterior myocardial infarction. There were no false positives when only true ventricular levels were used. A normal esophageal lead does not rule out the presence of posterior myocardial infarction. This was clearly shown in one of the post-mortem cases.

Deep Q waves were found in Lead III in many cases in which there was no evidence of posterior myocardial infarction. Conversely, some patients with posterior myocardial infarction showed normal Q waves in Lead III.

In some cases, no conclusion can be reached as to the condition of the posterior myocardium despite the study of Leads III, aV_F, and EV. Equivocal results were found in our series in patients with low voltage in Lead aV_F.

CONCLUSIONS

A comparative study was performed of the esophageal leads at ventricular levels with the standard and aV_F leads in the diagnosis of posterior myocardial infarction in a series of 100 patients, with Q waves in Lead III and/or abnormal T waves in Leads III and aV_F. The following conclusions were drawn:

1. The esophageal leads at ventricular levels were found to be valuable in the diagnosis of posterior myocardial infarction (64 cases).

2. In 12 per cent of the patients with posterior myocardial infarction, the esophageal leads did not demonstrate the lesion.

3. In 7 per cent of the patients with posterior myocardial infarction, the esophageal leads were the only ones which demonstrated abnormal Q waves, which were not present in aV_F.

4. No false-positive esophageal leads were found in normal patients.

5. A Q wave in the esophageal leads at ventricular levels which is greater than 25 per cent of the corresponding R wave probably indicates posterior myocardial infarction. The significance of this finding is enhanced if the Q wave is 4 mm. or more in amplitude, 0.04 second or more in duration, and if it is followed by a negative T wave.

6. Lead aV_F was more consistent than the esophageal lead in the indication of the presence of posterior myocardial infarction. However, some cases showed false positive Q waves in Lead aV_F.

7. Lead aV_F was more consistent than standard Lead III in the indication of posterior myocardial infarction.

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LATENT WOLFF-PARKINSON-WHITE SYNDROME

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THE mechanism responsible for the Wolff-Parkinson-White syndrome is still undetermined. The hypothesis most widely accepted at the present time—one proposed independently and almost simultaneously by Holzmann and Scherf[1] and by Wolferth and Wood[2]—attributes the syndrome to a congenital anomaly of conduction between auricles and ventricles over one or more muscular bridges of the kind originally reported by Kent, which function as accessory conduction pathways. This hypothesis has both experimental and histologic evidence to its credit.

Butterworth and Poindexter,[3] in experiments on animals, created an artificial accessory pathway by passing electrical impulses, picked up from the auricular surface, through a vacuum-tube amplifier to the ventricle and produced electrocardiograms very similar to the characteristic Wolff-Parkinson-White pattern. Then, reversing the connections and passing the ventricular impulses to the auricle, they induced paroxysms of auricular tachycardia like those that are a recognized part of the syndrome.

The accessory pathway hypothesis received further impetus when Wood and associates[4] demonstrated at autopsy the presence of muscular connections between the right auricle and right ventricle in the heart of a boy known to have had the syndrome during life. Several of these cases have now been autopsied and bridges found.

Although these histologic studies are important supportive evidence, enthusiasm has been tempered somewhat by the fact that Glomset and Glomset[5] had found muscular connections of the same sort in hearts that were presumably normal. Kent himself implied, though he did not so state, that these connections were found in all of the human hearts he examined, and referred to certain experiments and observations which led him to believe that such connections may function in man in certain instances.

There are, obviously, several gaps to be filled before this hypothesis can be considered fully established. No control study has been made to determine how frequently these muscular bridges occur in the human heart. No further experiments have been done to demonstrate that, when present, they can and do transmit impulses. No evidence has been presented to show that, if present and capable of transmitting impulses, they may fail to do so. It is with this last point that the present report is concerned.

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To explain the presence at autopsy of muscular bridges in hearts not known to have shown the syndrome during life, advocates of the accessory pathway hypothesis have suggested that the bridges may be present and lie dormant. It is well known that the electrocardiographic findings may be absent for limited periods of time. Anomalous conduction may change spontaneously to normal conduction and back again a number of times in the same record. Anomalous conduction can sometimes be abolished temporarily by appropriate measures, such as exercise, atropine, quinidine, or amyl nitrite. It is usually absent during an episode of auricular paroxysmal tachycardia. A series of electrocardiograms may show an occasional record with normal conduction throughout. There are several reports in which it is asserted that the syndrome (judging from the electrocardiogram) has been acquired or has been permanently suppressed as a result of various infectious or toxic illnesses or some remedial measure, such as tonsillectomy or thyroidectomy, but the observations appear to consist of only a few examinations over a short period of time.

None of the foregoing constitutes evidence to indicate that the accessory pathway may lie dormant for a considerable period of time. The only case fulfilling this condition found in an extensive, but not exhaustive, search of the literature is one presented by Öhnell[6] (his Case 69, Fig. 24). There was a history of recurrent attacks of paroxysmal tachycardia since 1912. An electrocardiogram in 1922 showed the Wolff-Parkinson-White pattern. Electrocardiograms made on one occasion in 1937 and once a month for six months in 1941 all showed normal conduction. In 1941, three days were spent in attempts to produce Wolff-Parkinson-White complexes, without success. The subject, nevertheless, continued to have troublesome attacks of paroxysmal tachycardia, often several times a week. The tachycardia was recorded on one occasion in 1941, and this record shows normal conduction. If, as has been suggested,[4,7] auricular paroxysmal tachycardia is initiated in these cases by an auricular stimulus conducted over the normal auriculoventricular pathway and returned to the auricle over the accessory pathway to set off a repetitive response there, one may surmise that the accessory pathway was still functioning from time to time. But the repeated electrocardiograms showing normal conduction suggest that it did lie dormant for a considerable portion of the time.

It is the purpose of this paper to present two additional cases that appear to fulfill this condition. One of them shows other features of interest, some of which we are unable to explain, but the case is presented in its entirety in the hope that it may have some bearing on the ultimate solution of the problem.

PRESENTATION AND DISCUSSION OF CASES

The first case, a 57-year-old man doing sedentary work, came to our attention on Sept. 13, 1939. He remained under our observation until April 1, 1947, when he was retired on disability because of Parkinson's Disease. He is still living but has not been examined by us since his retirement. The first electrocardiogram was made because of an elevated blood pressure, 184/90 mm. Hg. His blood pressure fluctuated thereafter between 138 and 170 systolic, and between 85 and 94 diastolic. There were no other pertinent findings. He had no cardiorespiratory symptoms except that he had noticed his heart "jumping" occasionally since childhood. He volunteered this information on our first examination. An electrocardiogram (Fig. 1), made a few minutes

later, showed one ventricular and five auricular premature beats in a one-minute run, together with three groups of two or three beats each, all in Lead *I*, which were interpreted as nodal rhythm. No premature beats were observed on any subsequent examination.

Nine electrocardiograms were made during the observation period of approximately seven and one-half years. In the record of Dec. 29, 1942, the fifth in the series, two consecutive complexes characteristic of the Wolff-Parkinson-White syndrome appeared in Lead *III* during deep held inspiration (Fig. 2). We were unable to reproduce this finding on subsequent examinations by the same maneuver. All of the electrocardiograms showed normal conduction throughout except for the findings described.

The second case, also a man doing sedentary work, came under our observation April 3, 1940, at the age of 25. He had consulted his family physician during an acute upper respiratory infection and was referred to us for an electrocardiogram because of irregular pulse. This physician had examined him many times before and had always found his pulse regular. The cardiovascular history was entirely negative. On some of our examinations, over the years, there has been a

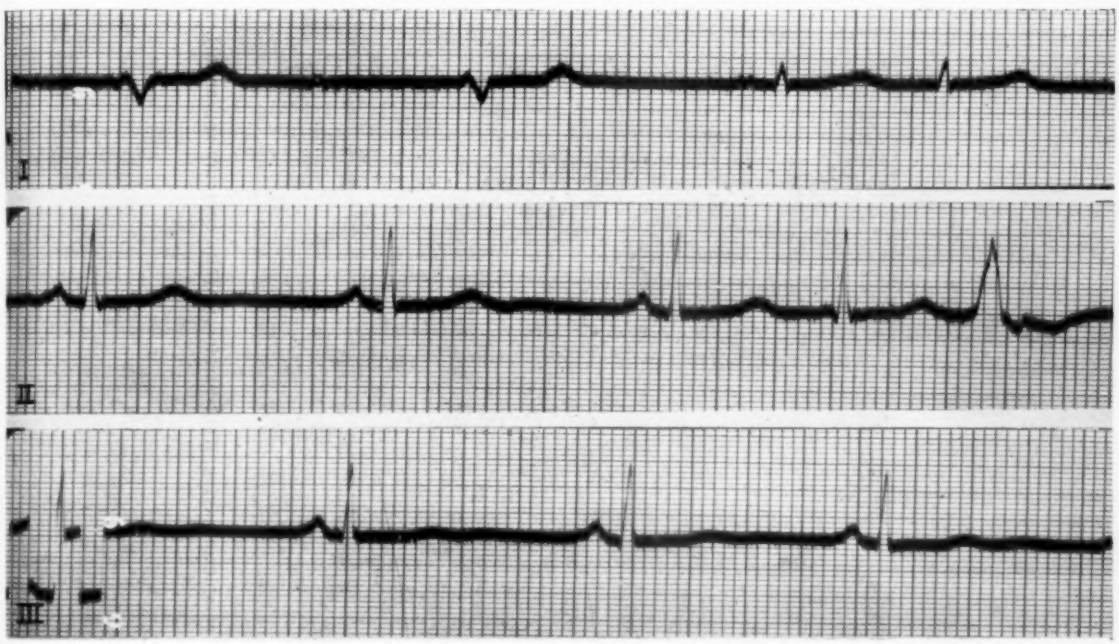

Fig. 1 (Case 1).—9/13/39. The first two complexes in Lead *I* were originally interpreted as nodal rhythm. In view of the two Wolff-Parkinson-White complexes that subsequently appeared in Lead *III* (Fig. 2), it seems possible that these also may represent the Wolff-Parkinson-White syndrome.

systolic murmur, usually at the apex but occasionally at the base; on some examinations no murmur could be heard. During the early part of the observation period, when the subject was admittedly apprehensive, the systolic blood pressure tended to be elevated and variable, with a high of 170 mm. Hg; more recently it has been normal. The pulse was grossly irregular on every examination from April 3, 1940, to Nov. 5, 1947. During the first few years of this period, the irregularity cleared after exercise and remained absent throughout two minutes of observation; later on, it could not be abolished.

Between April 3, 1940, and November 5, 1947, eighteen electrocardiograms were made. All of them showed frequent premature beats from multiple foci, occurring singly and in short runs. The runs consisted, usually, of two to four beats, involving one or more foci. The isolated premature beats were sometimes interpolated, sometimes followed by a pause. A great variety of ventricular complexes was recorded. All of the distinctly different types, and some of the minor variations, are shown in Figs. 3, 4, and 5; these strips have been selected to avoid the runs, as far as possible, so that the contours can be more easily distinguished. Contours that occurred

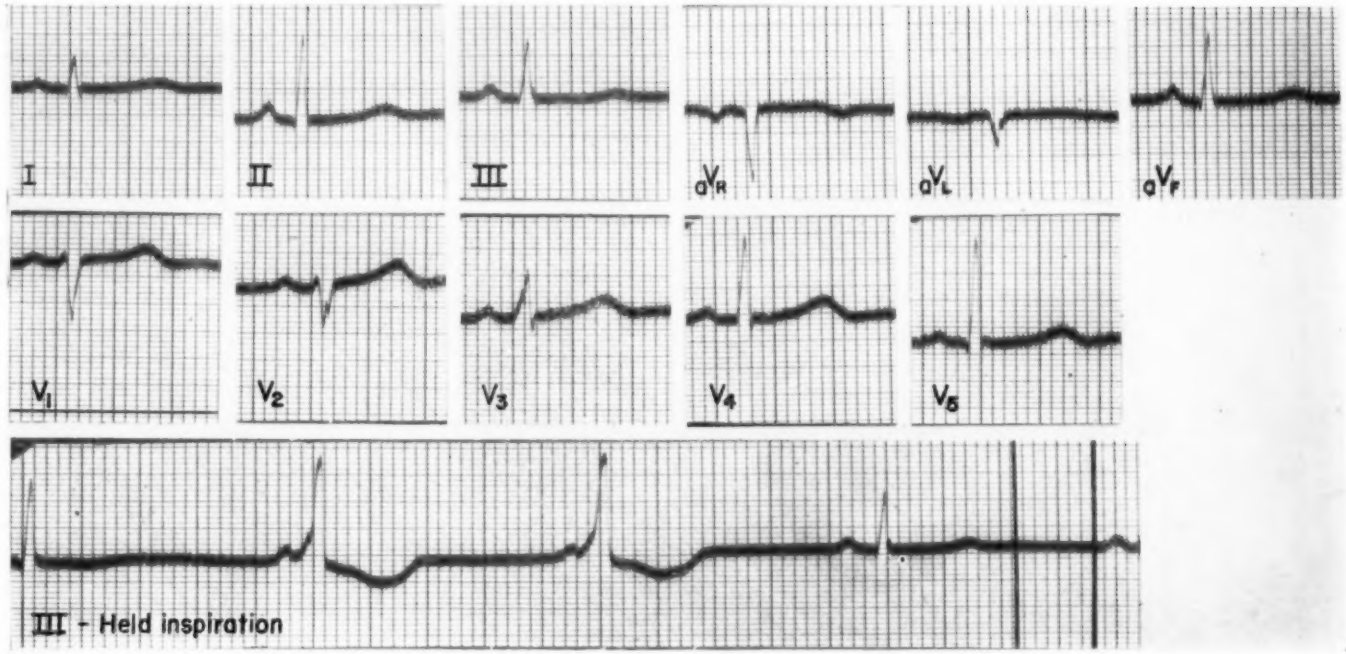

Fig. 2 (Case 1).—12/29/42. Two complexes having Wolff-Parkinson-White contours appear in Lead *III* during deep held inspiration.

repeatedly on one examination might be absent altogether on another. One or more auricular and two to four ventricular foci appeared to be active in each record. An occasional auricular premature beat had a prolonged P-R interval. There have been pauses, now and then, interpreted as sinoauricular block. All of the sinus beats showed normal conduction.

On Nov. 5, 1947, the subject reported that in July of that year he had had several attacks of rapid heart action which started suddenly and stopped suddenly. They lasted from two minutes to five hours, usually about two hours, and were accompanied by discomfort in the sternal region. There was no angina of effort. The attacks ceased after a short course of quinidine therapy and had not recurred. The electrocardiogram made Nov. 5, 1947, is shown in its entirety (Fig. 6). It will be noted that the sinus beats still show normal conduction. The irregularity now consists almost exclusively of runs of premature beats in contrast to previous records,

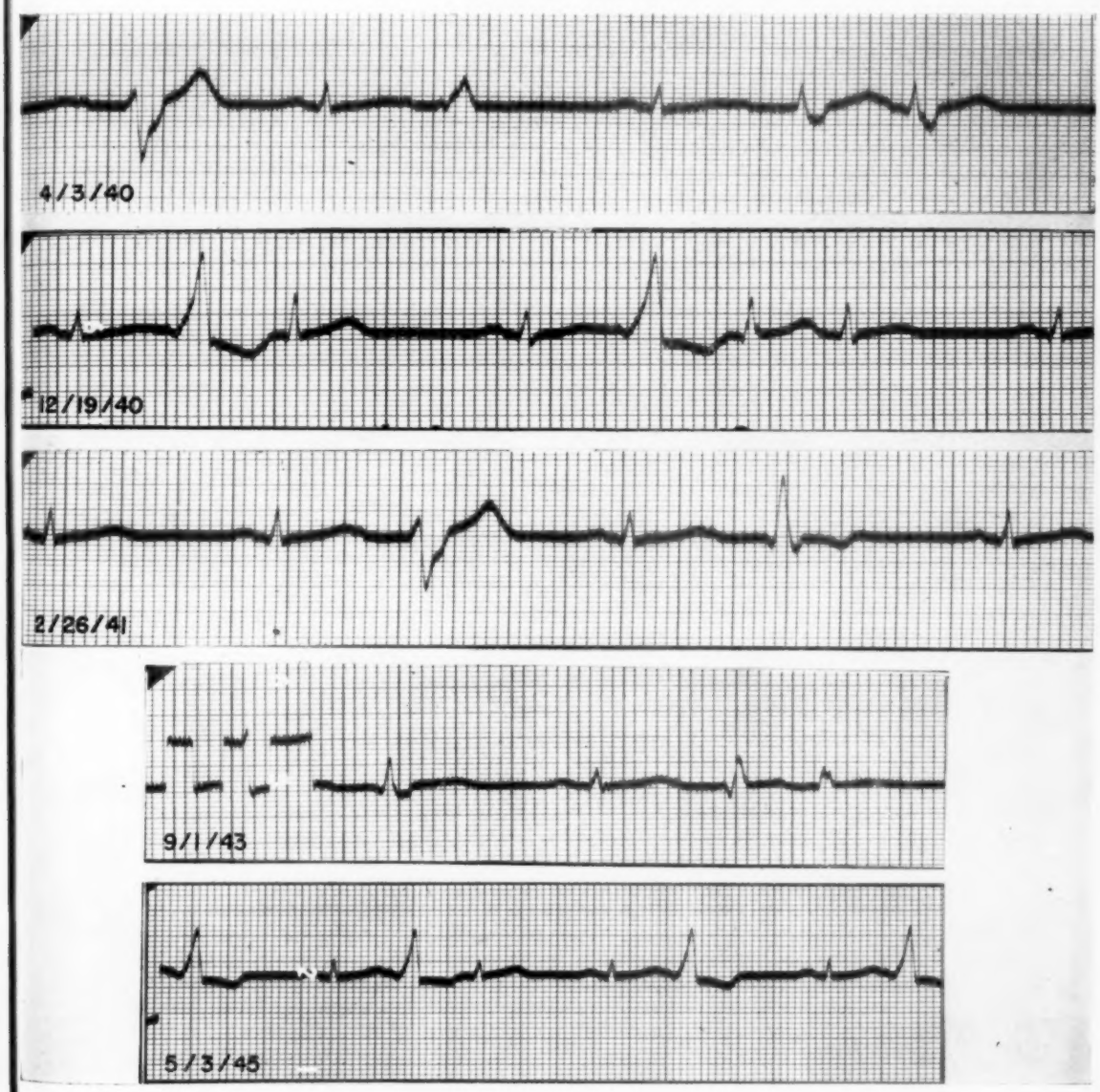

Fig. 3 (Case 2).—Strips of Lead *I* recorded at various times from April 3, 1940, to Nov. 5, 1947, and selected to show the various types of aberrant ventricular complexes.

Fig. 4 (Case 2).—Strips of Lead *II* recorded at various times from April 3, 1940, to Nov. 5, 1947, and selected to show the various types of aberrant ventricular complexes.

in which many of the premature beats occurred singly. All of the aberrant ventricular contours in this record had been present in the previous records. These findings are of particular interest in view of subsequent developments.

On Jan. 15, 1948, he came to the Medical Department and gave the following history. In the latter part of December, the attacks of rapid heart action had begun again and had occurred almost daily since that time. That morning of Jan. 15, 1948, he was awakened at 1:00 A.M. by

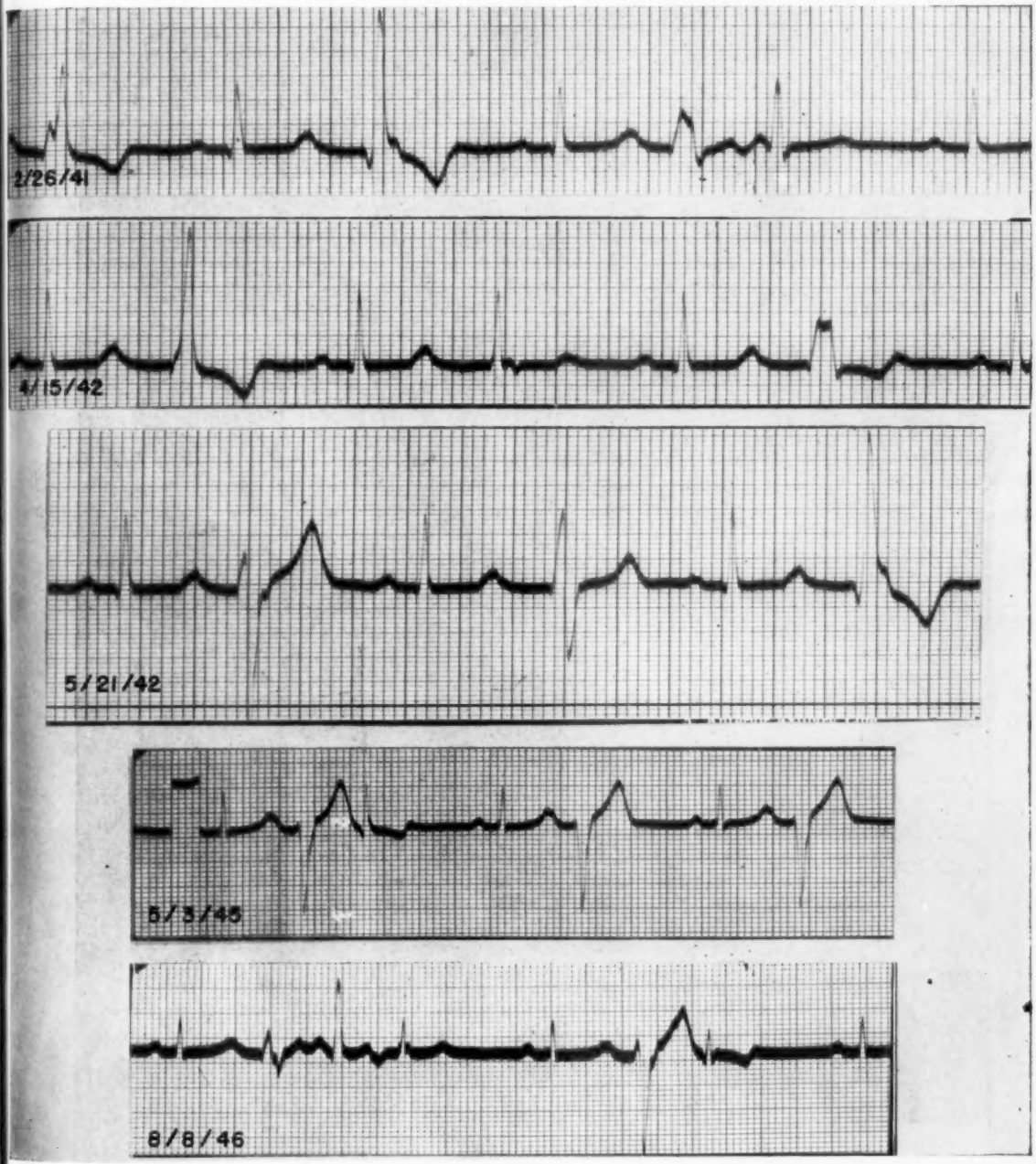

Fig. 5 (Case 2).— Strips of Lead *III* recorded at various times from April 3, 1940, to Nov. 5, 1947, and selected to show the various types of aberrant ventricular complexes.

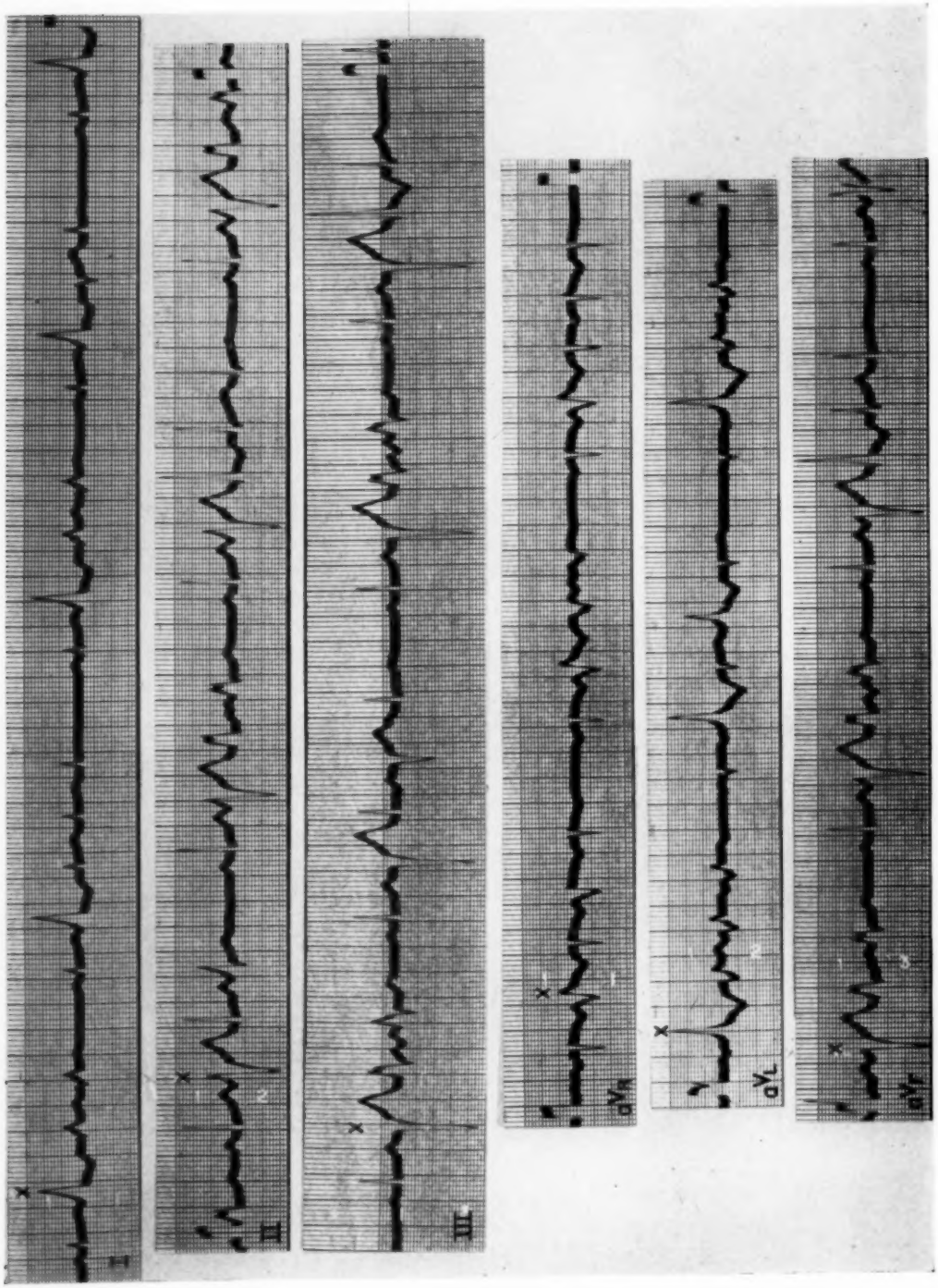

Fig. 6A.

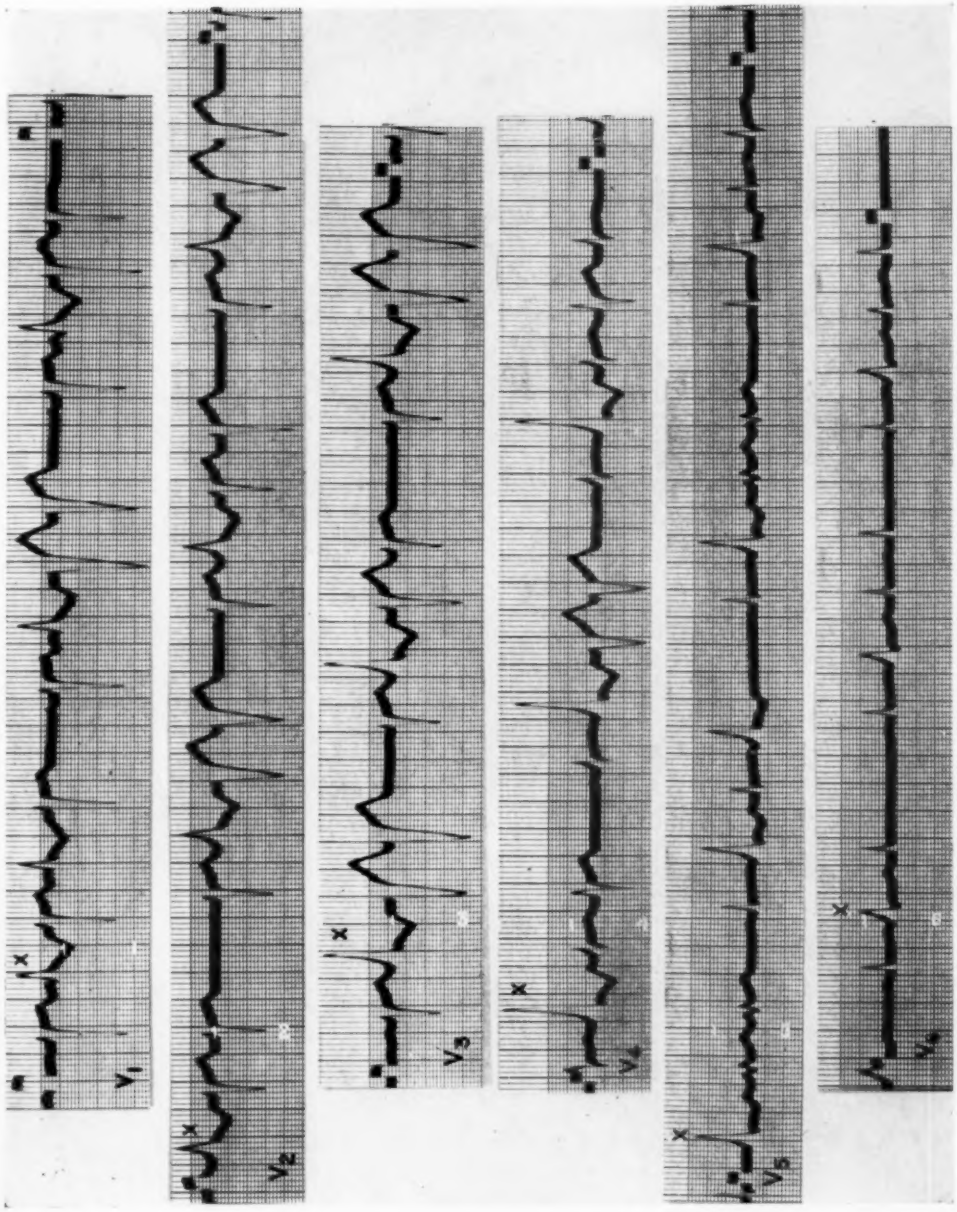

Fig. 6A.

Fig. 6B.

Fig. 6 *A* and *B* (Case 2).—11/5/47. Numerous short runs of premature beats with a variety of ventricular complexes, all of which had been present from time to time on the seventeen previous electrocardiograms.

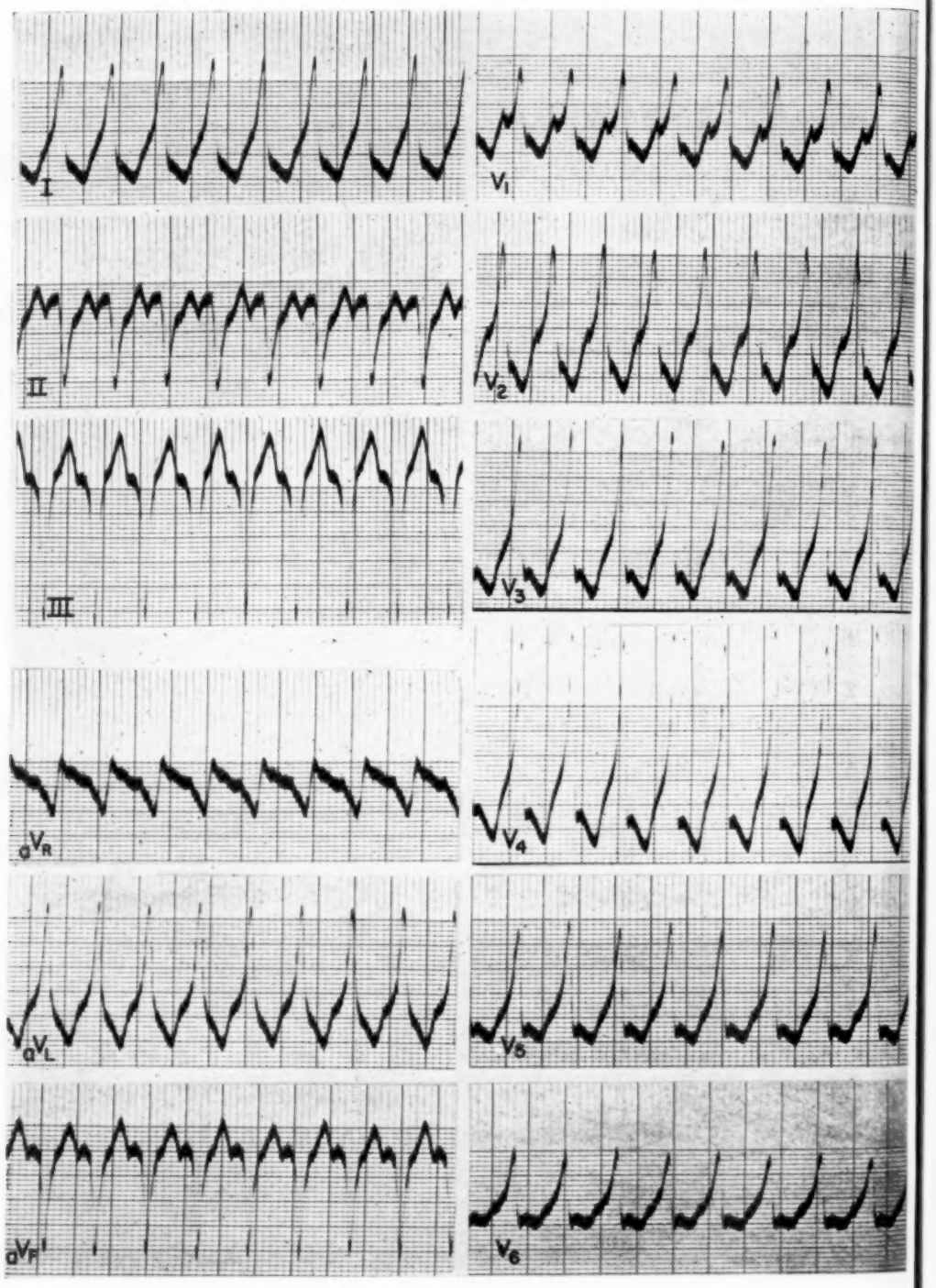

Fig. 7 (Case 2).—1/15/48, 10:30 A.M. Paroxysmal tachycardia. QRS complexes, lead for lead, are essentially the same as those marked *x* in the record of 11/5/47 (Fig. 6).

an attack which stopped spontaneously at 5:00 A.M. Another attack began at 9:00 A.M. and was still continuing. On examination, the pulse was very rapid, and the systolic blood pressure 76 mm. Hg; the diastolic could not be determined. An electrocardiogram, made at 10:30 A.M., showed paroxysmal tachycardia (Fig. 7). At 11:00 A.M. he was given 6 grains of quinidine sulphate and put on a cot to rest. The attack ceased at 12:10 P.M. He continued to rest until 1:30 P.M., when another electrocardiogram was made (Fig. 8). It showed the Wolff-Parkinson-White syndrome with occasional auricular premature beats—eight in a forty-five second recording. Seven subsequent electrocardiograms have been made, all of which show the Wolff-Parkinson-White syndrome (alternating, in the two most recent records, with normal conduction).

The electrocardiographic events merit careful study. The tachycardia shown in Fig. 7 is somewhat confusing. The QRS-T contours suggest that it is ventricular in origin, and this view is supported by the fact that the ventricular complexes are, with some allowance for disturbance in conduction because of the rapid rate, quite similar in every lead to the complexes marked *x* in the preceding record (Fig. 6). These same contours had appeared occasionally in the electrocardiograms made previously, singly or in pairs, and were thought to be ventricular premature beats. But one of the essentials for a diagnosis of ventricular paroxysmal tachycardia is lacking: no P waves can be distinguished coming at a slower rate than the QRS complexes.

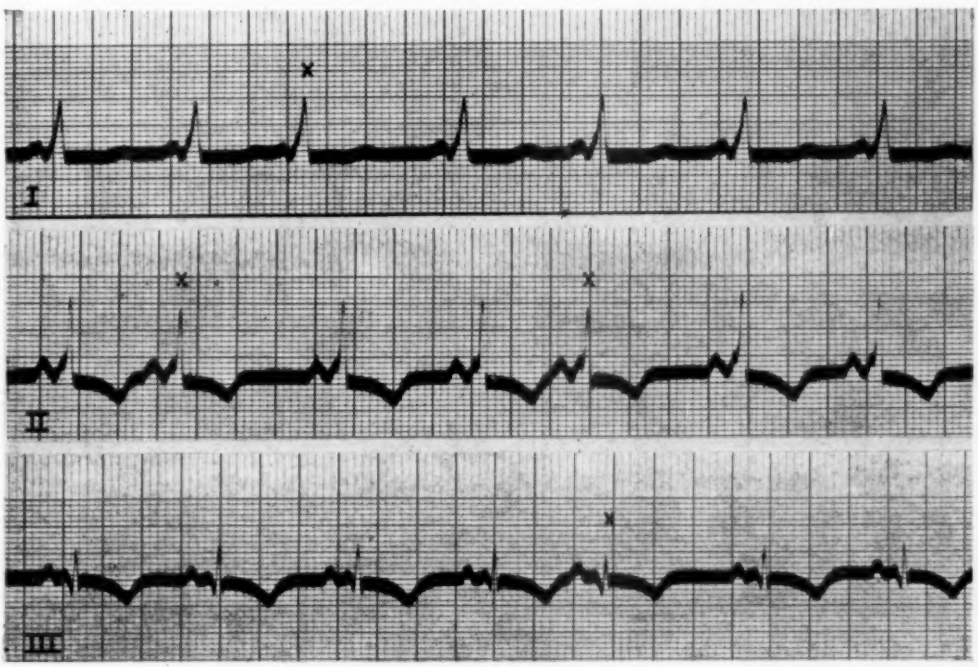

Fig. 8 (Case 2).—1/15/48, 1:30 P.M. **Wolff-Parkinson-White syndrome with occasional auricular premature beats.**

An electrocardiogram made on the next examination, Feb. 2, 1948, (Fig. 9) provides the solution. It shows the Wolff-Parkinson-White syndrome, broken by many short runs of tachycardia and several single premature beats with the same ventricular contours that were present in the continuous tachycardia of Fig. 7. It is now clear that the tachycardia is auricular in origin. With several successive sinus beats present between paroxysms, it can be seen that the T waves of the sinus beats immediately preceding the onset of tachycardia are larger than the T waves of the remaining sinus beats, and this is most conspicuous in the leads where the P waves are largest. These are obviously P waves superimposed on the preceding T waves, so that the tachycardia begins with a premature auricular contraction. The beats constituting the runs, likewise, have a P wave superimposed on every T wave except the last. The single beats with the same contour, also, closely follow a sinus beat and have a premature P wave.

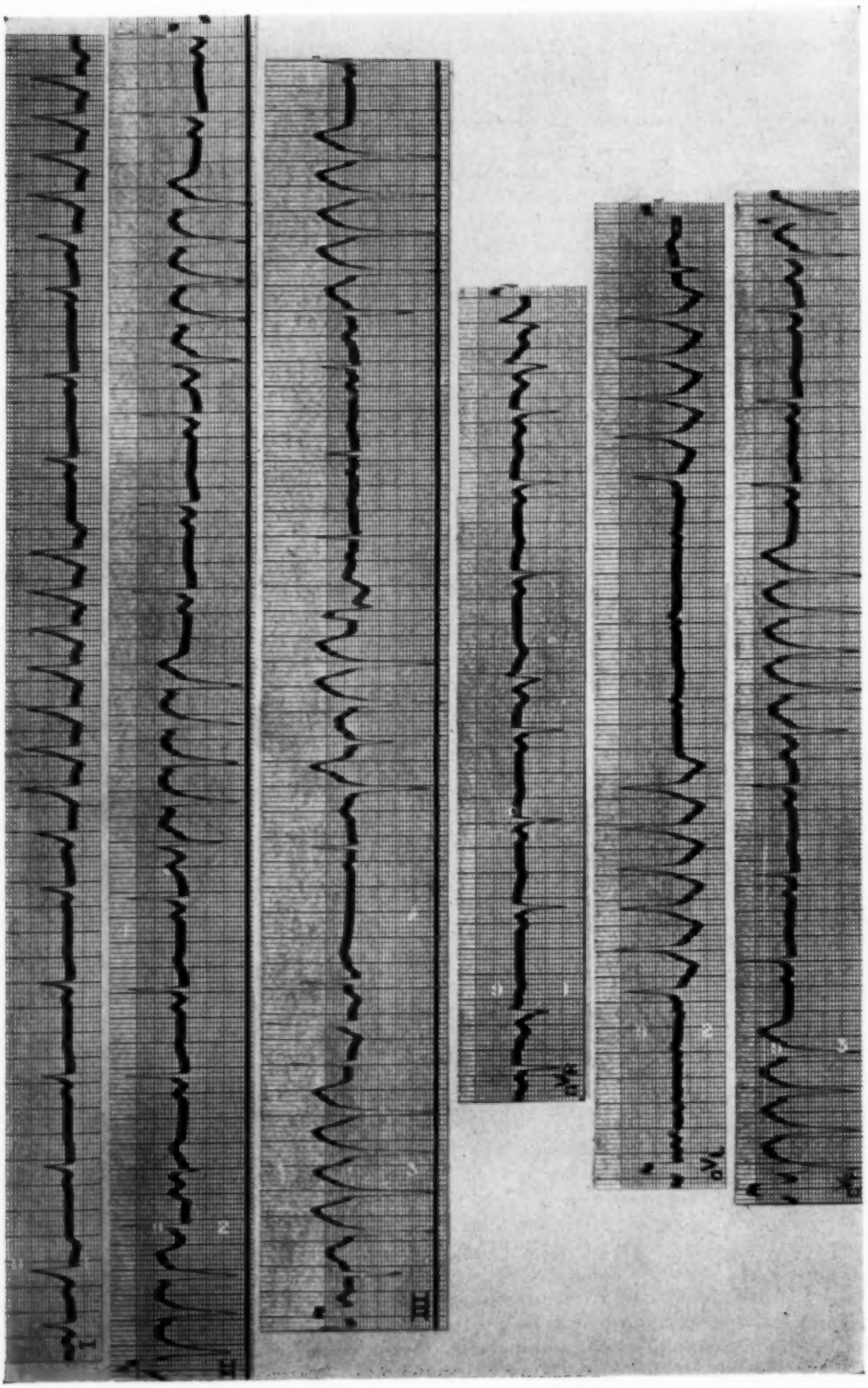

Fig. 9A.

Fig. 9 *A* and *B* (Case 2).—2/2/48. Wolff-Parkinson-White syndrome, broken by short runs of tachycardia and single premature beats with the same ventricular contours as the continuous tachycardia recorded on 1/15/48 at 10:30 A.M. (Fig. 7).

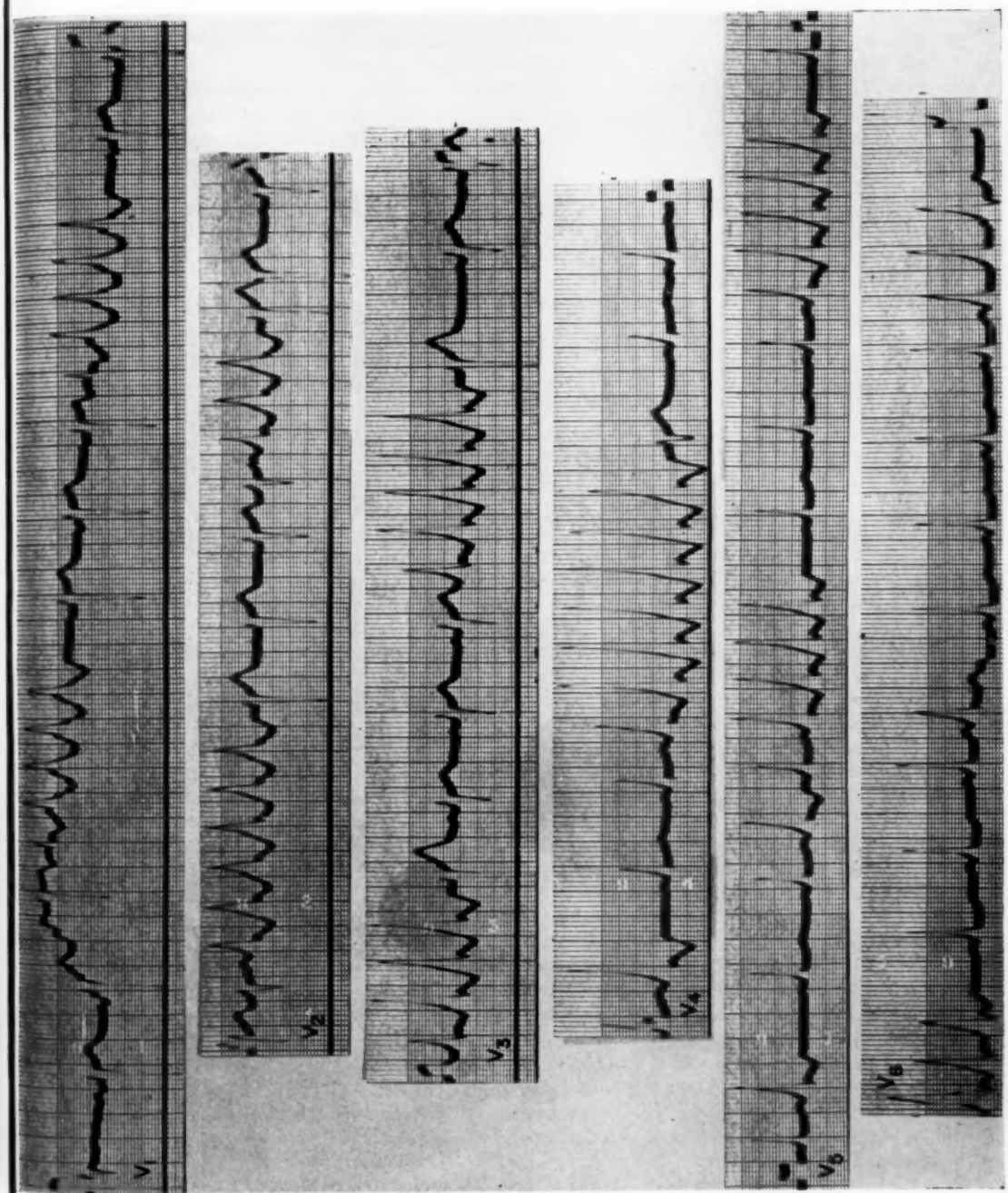

Fig. 9B.

It is noted, further, that although the runs sometimes terminate with a few rapid beats of different contours, some of which may be ventricular premature beats, they are never initiated by a beat from a ventricular focus. Examination of all previous electrocardiograms in which beats with this contour occur—whether single, coupled, or in runs—shows that they were always preceded by a beat of supraventricular origin. This is especially striking in the record of Nov. 5, 1947, (Fig. 6): whenever a beat with this contour occurs a second time during a run (as it does in Leads *III*, aV_R, aV_L, V_1, and V_5) it invariably follows a beat of supraventricular origin.

A beat of supraventricular origin preceding the onset is consistent with and a necessary condition for the auricular paroxysmal tachycardia characteristic of the Wolff-Parkinson-White syndrome according to the theory as stated by Wood and associates[4] and by Scherf and associates.[7] They believe that occasionally an auricular stimulus transmitted through the normal conduction system is immediately transmitted back to the auricle over the accessory pathway. Any stimulus so applied at the end of systole or in early diastole may lead to ectopic stimulus formation with repetitive response, that is, auricular paroxysmal tachycardia under the conditions assumed. But if the stimulus originated in the ventricle and if it were reversedly transmitted to the auricle and then back to the ventricle over the accessory pathway and set up a repetitive response, the result would be ventricular paroxysmal tachycardia. Although the paroxysmal tachycardia of the Wolff-Parkinson-White syndrome has often been recorded electrocardiographically, the beginning and end of the paroxysms have seldom been recorded, so that little opportunity has been afforded to study this point.

Still another significant feature is more readily seen in this record (Fig. 9), where the tachycardia is less rapid than before and where there are isolated premature beats of the same form: namely, that the tachycardia itself is characteristic of the Wolff-Parkinson-White syndrome. This is most clearly evident in Lead I and in the left precordial leads. Moreover, its contours are distinctly different from those of the Wolff-Parkinson-White recorded at the normal rate. A clue to the explanation lies in V_1, where QRS complexes are upright during the tachycardia and are mainly inverted when the rate is slow. Rosenbaum and associates[8] noted these two types of complexes in the right precordial leads, and divided their cases of the Wolff-Parkinson-White syndrome into two groups on that basis. After detailed analysis of leads made from various parts of the thorax and the esophagus, they concluded that the differences were due to a difference in the location of the ventricular end of the accessory pathway. They reported one case (their Case 10) showing, as ours does, both types of complexes, which they believed due to the presence of two accessory pathways in different locations.

The view that two accessory pathways are present is supported in our case by the fact that the electrical axis during the runs of tachycardia is quite different from the electrical axis when either the Wolff-Parkinson-White syndrome at the slower rate or normal conduction is present—there being a marked left axis deviation during the tachycardia and a tendency to right axis deviation in the other two. It will be remembered that Butterworth and Poindexter,[3] in their experimental production of the Wolff-Parkinson-White syndrome, obtained left axis deviation when they stimulated the right ventricle and right axis deviation when they stimulated the left ventricle. Histologic studies have demonstrated that more than one pathway may be present and that they are not always located at the right lateral heart border. They have been found in the septum[9] and in the free wall of the left ventricle.[6] In Öhnell's[6] case (his Case 11, Figs. 14 C and D), where a muscular bridge was found in the dorsal portion of the left ventricle about 4 cm. from the septum, the electrocardiogram showed no axis deviation during sinus rhythm, but during paroxysmal tachycardia showed a marked right axis deviation with wide, bizarre QRS complexes resembling the Wolff-Parkinson-White pattern. Wood and associates[4] found three bridges, close together, in the right lateral heart border in their case, and the electrocardiogram showed a marked left axis deviation. One might speculate, in our case, that one bridge is near the auriculoventricular node, and the other (the one functioning during tachycardia) is in the free wall of the right ventricle some distance away.

A review of the electrocardiograms in the literature reveals that none of the features in our case is unusual. The electrical axis is virtually the same during normal and anamalous conduction in some cases and quite different in others. In most cases the ventricular complexes during tachycardia are like those during normal conduction, and the auricular impulses are assumed to

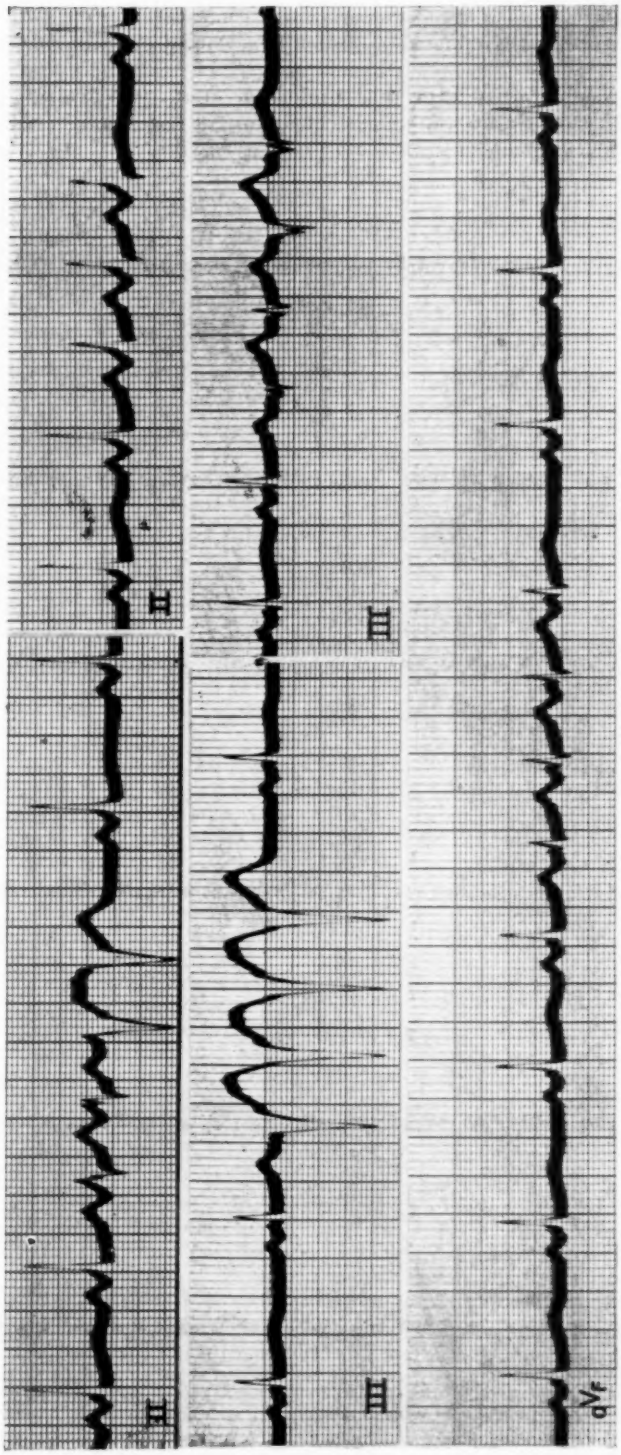

Fig. 10 (Case 2).—4/7/48. Wolff-Parkinson-White syndrome, broken by short runs of tachycardia showing both types of Wolff-Parkinson-White complexes. Only Leads *II*, *III*, and *a Vf* are illustrated.

be transmitted through the normal conduction system; but in some cases the tachycardia is like the Wolff-Parkinson-White pattern, and transmission is presumed to be through the accessory pathway.

The next record, made April 7, 1948, (Fig. 10) also shows the Wolff-Parkinson-White syndrome with isolated premature beats and frequent short runs of tachycardia. Some of the runs are like the Wolff-Parkinson-White of the sustained tachycardia (Fig. 7), and some are more like

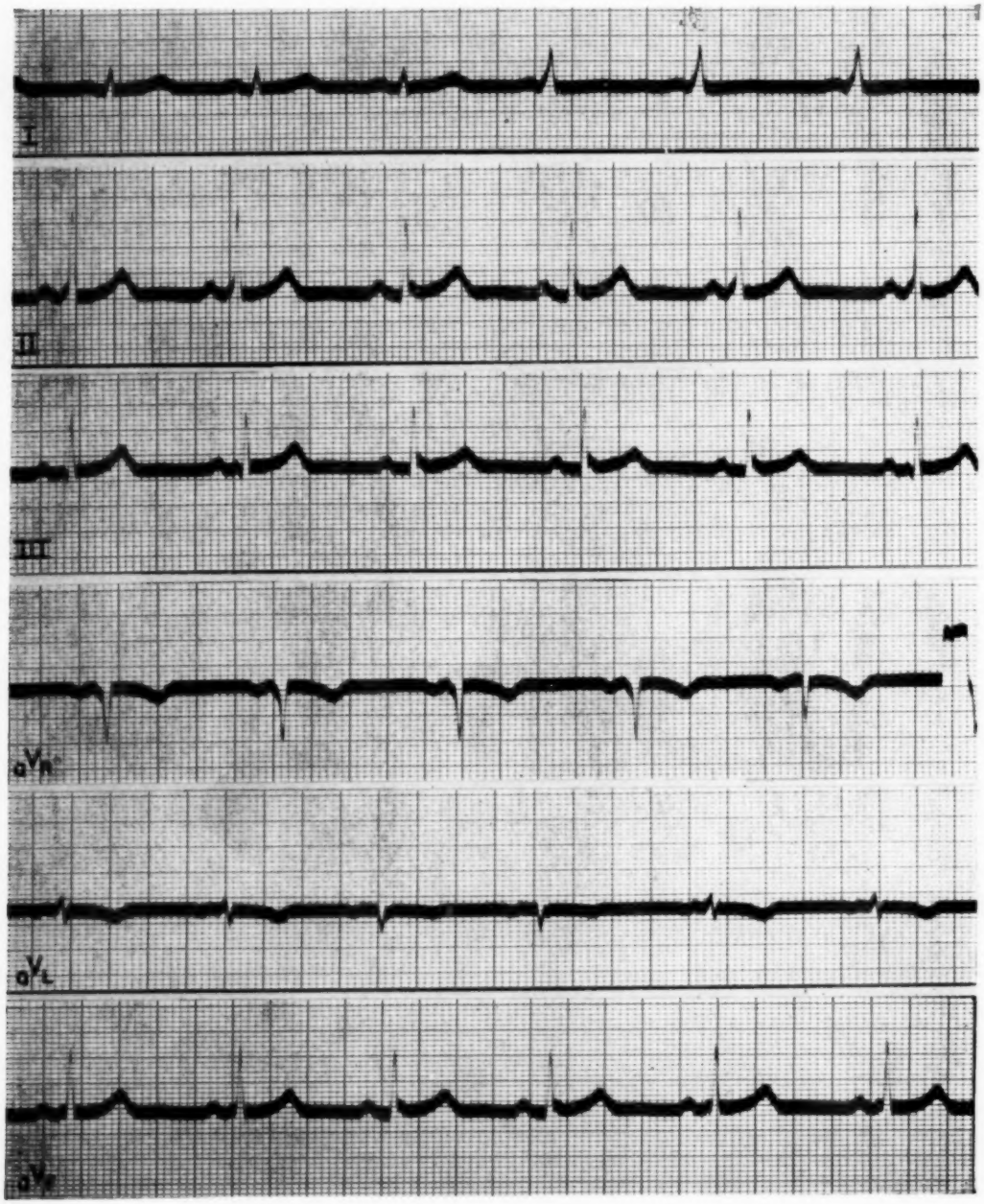

Fig. 11*A*.

Fig. 11 *A* and *B* (Case 2).—9/23/52. Spontaneous changes from Wolff-Parkinson-White syndrome to normal conduction.

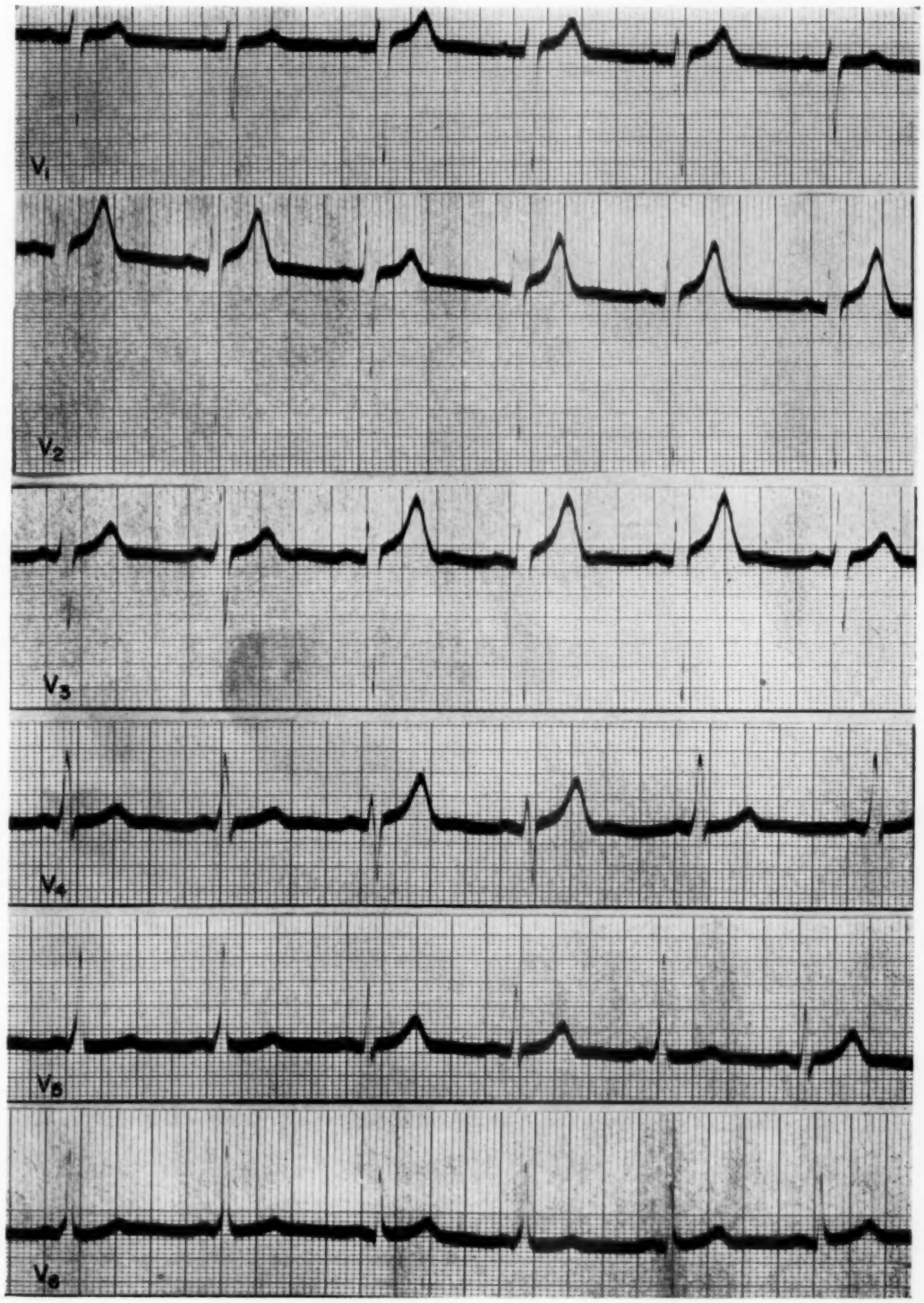

Fig. 11*B*.

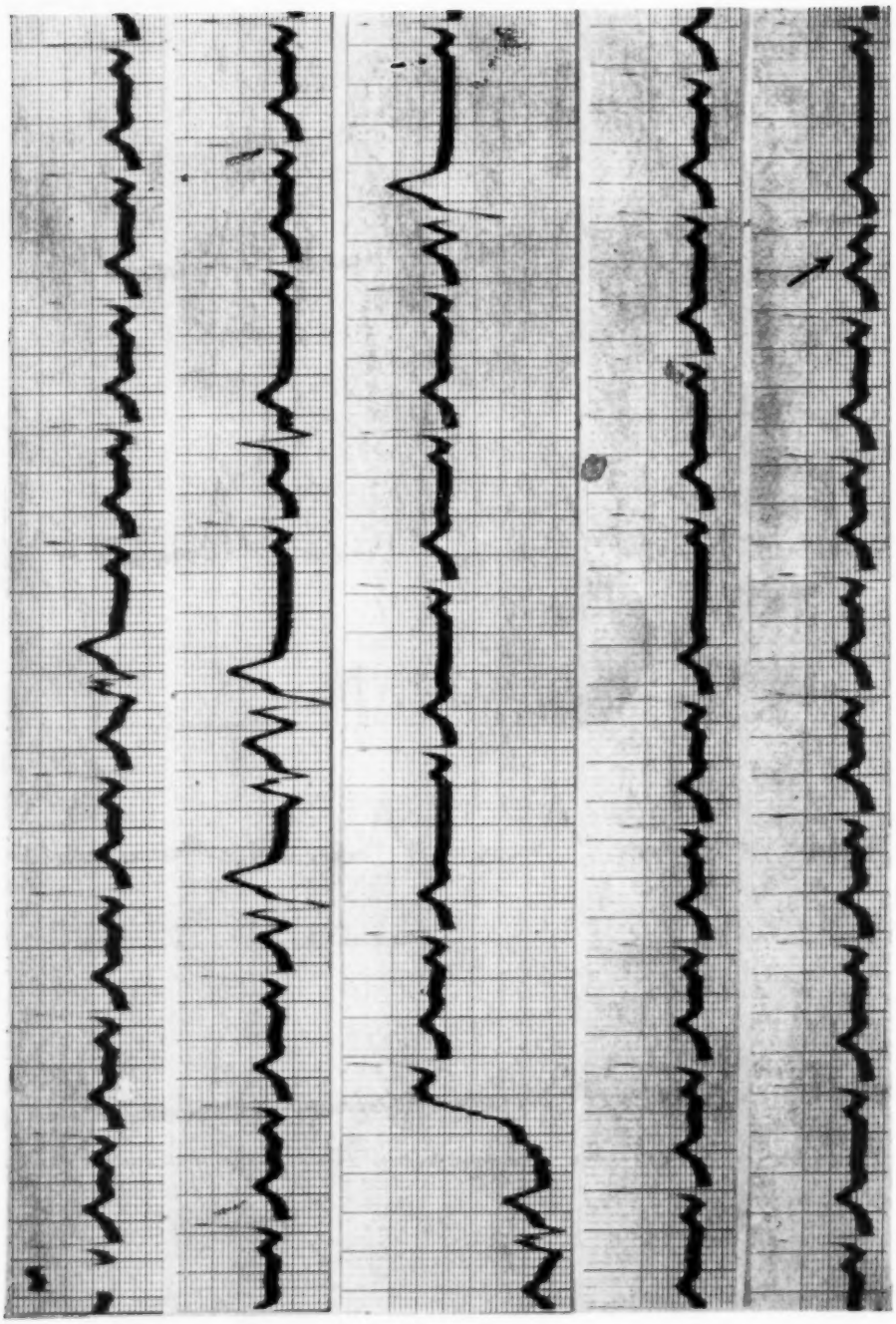

Fig. 12A.

Fig. 12 *A* and *B* (Case 2).—9/23/52. Continuous one-minute run on Lead *II* after exercise, showing premature beats with aberrant ventricular contours.

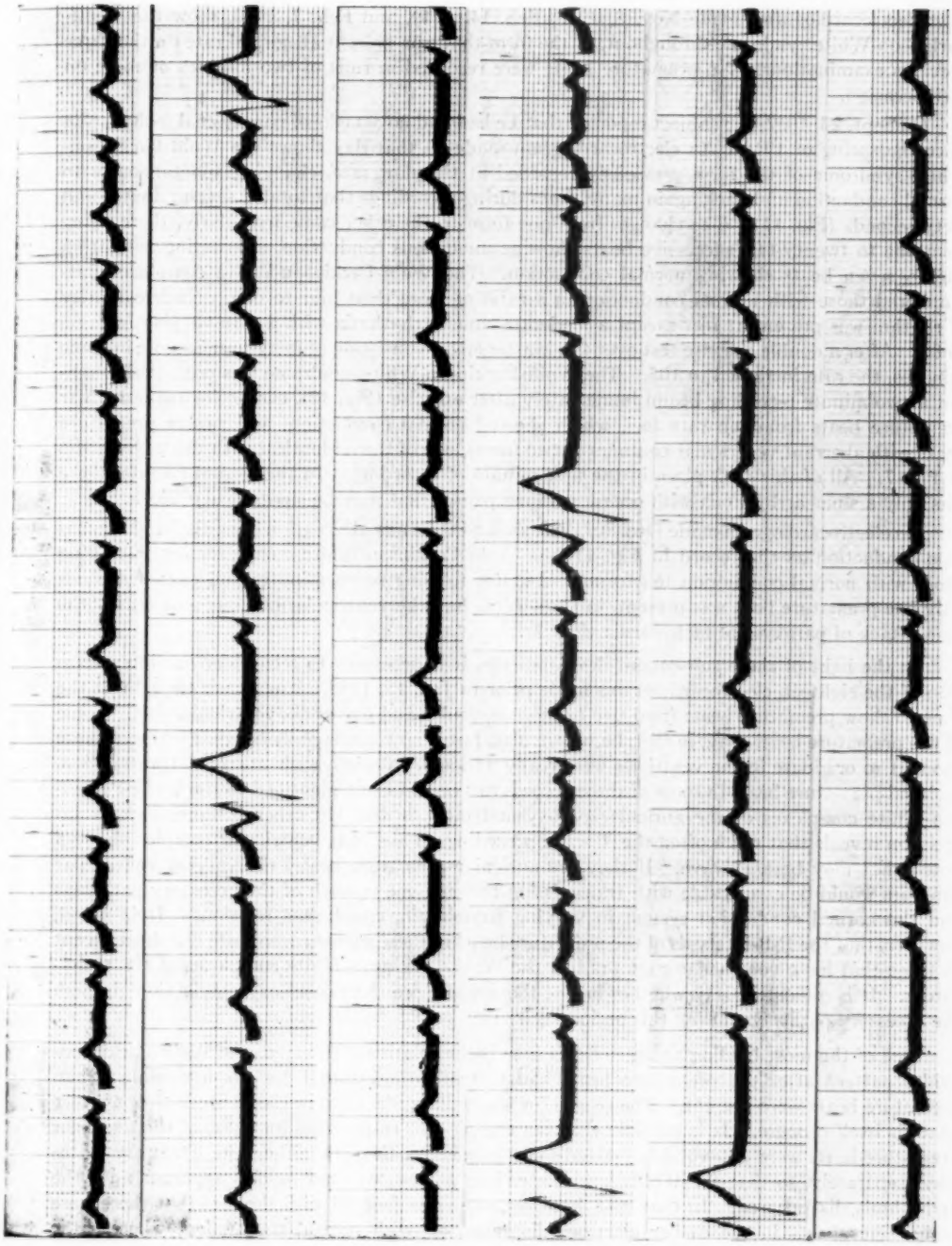

Fig. 12*B*.

the Wolff-Parkinson-White at the normal rate. Both include a few aberrant ventricular complexes of various forms that were recorded during the period of April 3, 1940, to Nov. 5, 1947.

Electrocardiograms made Nov. 8, 1948, Feb. 14, 1949, and Feb. 7, 1950, show the Wolff-Parkinson-White syndrome throughout, of the form that was present at normal rate on the three previous examinations. No premature beats were recorded in runs of two minutes or more on each occasion.

On Sept. 23, 1952, the subject reported that he had had no attacks of paroxysmal tachycardia since the spring of 1948. An electrocardiogram made on that day shows the Wolff-Parkinson-White syndrome of the form previously recorded at the slow rate, changing spontaneously to normal conduction and back again many times during recordings that totaled seven minutes and forty seconds (Fig. 11). The changes from one form to the other came irregularly, there being from one to twenty-two successive beats showing anomalous conduction, alternating with from one to seven beats showing normal conduction. The Wolff-Parkinson-White complexes outnumbered those with normal conduction in a ratio of more than four to one. No irregularity of rhythm was present at rest except a moderate sinus arrhythmia with a rate varying from 66 to 80. After a double exercise test over the Master steps, consisting of forty-four ascents in three minutes, the rate increased to 105. The Wolff-Parkinson-White syndrome was present throughout a two-minute recording begun immediately after exercise (Fig. 12), except for two auricular premature beats from separate foci, which showed normal conduction, and twelve premature beats with aberrant ventricular contours of two forms, one of them identical with the tachycardia of Fig. 7. All of this took place in the first minute of recording. In the second minute, there was only a sinus arrhythmia with occasional long pauses that may be sinoauricular block.

An electrocardiogram made Dec. 30, 1952, showed the same alternation of normal and anomalous conduction as the record in Fig. 11, the Wolff-Parkinson-White complexes outnumbering those with normal conduction ten to one. In runs totaling seven minutes and twenty seconds only one premature beat was present, in Lead *II*; it had the ventricular contour seen during the long attack of paroxysmal tachycardia (Fig. 7).

In the light of these subsequent developments, it is necessary to reconsider our interpretation of the eighteen electrocardiograms made prior to Jan. 15, 1948. They were thought at the time to show premature beats from two or more auricular and five or six ventricular foci. Some of the premature beats may, in fact, be ventricular, but it now seems probable that many of those thought to originate in the ventricles were really auricular in origin with aberrant transmission. Isolated premature beats in some of these records can be definitely identified as the Wolff-Parkinson-White complexes of the auricular paroxysmal tachycardia. In other instances, closer inspection reveals that quite often the T wave preceding an aberrant ventricular complex shows a notch that may be a P wave. If they are auricular premature beats, the varying ventricular contours would be compatible with transmission through one or both of the accessory pathways and the normal conduction system in varying combinations and time relations. It is noted, however, that the P-R intervals of the premature beats in these earlier records are not short except in those that have ventricular contours like the Wolff-Parkinson-White complexes of the tachycardia. It is difficult to say whether or not there was more than desultory conduction through the accessory pathways during this period.

One of the most baffling aspects of this case is the relative stability of the Wolff-Parkinson-White pattern after the premature beats had virtually disappeared and its instability when premature beats were present. The reason for the striking decrease in the number of premature beats is itself obscure. It is possible that the ectopic foci responsible for most of the auricular premature beats were unfavorably located for transmission through either the accessory pathways separately, so that the Wolff-Parkinson-White pattern was not readily apparent until the arrhythmia disappeared. In that case, however, one is confronted with the fact that there were many sinus beats in the earlier electrocardiograms, all with normal conduction, whereas the sinus beats showed anomalous conduction after the arrhythmia disappeared. On the other hand, if, for some reason, one of the accessory pathways and the auricular foci became depressed, why should the other pathway become more excitable? This is a feature for which we have found no satisfactory explanation.

CONCLUSION

In Case 1, it must be concluded that the underlying condition capable of producing the Wolff-Parkinson-White syndrome was present and lay dormant for a considerable period of time if it is conceded that the two complexes recorded in Lead *III* on Dec. 29, 1942, (Fig. 2) are the Wolff-Parkinson-White syndrome. The strongest argument for believing them to be so is that they have the characteristic Wolff-Parkinson-White contour. Similar contours might conceivably be produced by the discharge of a ventricular ectopic focus after the P wave has been written, but two successive ectopic beats of this kind usually occur in rapid succession, resulting in coupling. In this instance there is no significant change in the basic rhythm. In retrospect it seems possible that the three brief runs recorded in Lead *I* on Sept. 13, 1939, (Fig. 1), which were interpreted as nodal rhythm, might also have been the Wolff-Parkinson-White syndrome, although the contours are not so clearly characteristic in this lead.

In Case 2 the situation is more complicated. We do not know whether or not the Wolff-Parkinson-White syndrome was present during the first twenty-five years of the subject's life. No electrocardiograms were made prior to April 3, 1940. There is no history of paroxysmal tachycardia or even of irregular pulse before that time, but this cannot be taken as evidence that anomalous conduction was absent, since no premature beats were recorded in several recent electrocardiograms which show the Wolff-Parkinson-White syndrome throughout.

During the period from April 3, 1940, to Jan. 15, 1948, the presence of the Wolff-Parkinson-White mechanism was not suspected. It now seems possible that transmission passed frequently back and forth between the normal conduction system and some aberrant route which included one or more accessory pathways. But during this period there was no continuously sustained transmission through the accessory pathways, since there were many sinus beats with normal conduction and many supraventricular premature beats with normal conduction time.

The most convincing evidence is to be found in the period from Jan. 15, 1948, to date. If we are correct in believing that two accessory pathways are present in this case, it seems justifiable to assume that the one producing the aberrant ventricular complexes during auricular tachycardia lies dormant when normal rhythm is present. The recent history and examinations suggest that this may be for considerable periods of time.

Despite the uncertainties in Case 2, we believe that these two cases do show that the mechanism capable of producing the Wolff-Parkinson-White syndrome may be present and lie dormant. If it is finally established that muscular bridges between auricles and ventricles are responsible for the anomalous conduction, evidence of the kind presented here will be necessary to reconcile the presence of the muscular bridges at autopsy in hearts never known to have shown the syndrome during life.

SUMMARY

Two cases are presented which show presumptive evidence that the mechanism producing the Wolff-Parkinson-White syndrome may lie dormant for considerable periods of time. The observations reported may be of importance in ultimately explaining this phenomenon.*

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*The observations reported here have been offered in support of the accessory pathway hypothesis. They contribute nothing to the irritable focus theory, either to confirm or disprove it, since irritable foci are notably temperamental in performance.

PHYSICAL BASIS OF THE LOW-FREQUENCY BALLISTOCARDIOGRAPH

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UTRECHT, HOLLAND

THE circulation of the blood is a mechanical phenomenon in which the heart has the task of keeping this circulation going. The forces appearing in the body of man and animal displace the blood.

Ballistocardiography makes the attempt, by means of observation and analysis of the forces, the velocities, or the mass displacements, to gather information about the circulation, in particular of the stroke volume and of abnormalities of the heart or the large blood vessels. Several methods have already been developed for the recording of one of the three quantities: force, velocity, or mass displacement. The original model of Gordon[5] recording mass displacement was very simple: a light bed swung by four ropes from a trestle. Because the absence of damping of this "swing" and the respiration of the patient lying on it caused almost insurmountable difficulties, later investigators (Starr and associates[10] and Nickerson and Curtis[9]) proceeded to build their ballistocardiographs in a different way. They no longer recorded mass displacements. The original difficulties have been replaced by other ones, which made the analysis of the obtained curve more difficult and the apparatus more complicated.

As our aim is to develop a method that is physically understandable and reliably based we have again taken up the original, simple, and clear method of Gordon[5] and Henderson.[7]

In the following this "real" low-frequency method will be explained and its practical advantages will be accounted for.

MECHANICS OF THE BALLISTOCARDIOGRAPH

A system (e.g., a patient) is conceived of that is unaffected by external forces. If the body (mass m_1) exerts a force (K_1) on an amount of blood (mass m_2), then, according to the law of action and reaction, this amount of blood will exert an equal, but opposite, force (K_2) on the body. So we have: $K_1 = -K_2$ or $K_1 + K_2 = 0$. With $K = ma$, in which a is the acceleration, mass m obtains as a result of action of K, this will yield $m_1a_1 + m_2a_2 = 0$. From this it follows that $m_1v_1 + m_2v_2 = c$, in which v_1 and v_2, respectively, are the velocities by which

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the masses m_1 and m_2 move as a result of the action of K_1 and K_2; c is a constant. From the last equation it follows that:

$$m_1x_1 + m_2x_2 = ct + d \qquad (1)$$

in which x_1 and x_2 are the respective displacements of m_1 and m_2, d is a constant and t the time. If the initial velocity of the entire system is zero, then $c = 0$, that is, the center of gravity keeps the same position. We have here an infinitely rapid reaction, since at any moment $m_1x_1 + m_2x_2 = d$ is exactly fulfilled.

In reality there is always a damping causing c to become 0, so the common center of gravity of body and blood has a fixed position in space.

If we imagine a patient on whom no external forces are exerted and who, therefore, is suspended freely, the displacement of the center of gravity of the blood with respect to its surroundings could be measured. Such a freely suspended system cannot be realized. It can be approximated, however, by admitting a weak binding of the system with its surroundings. If this binding of the system with its surroundings is stronger, something else can be measured instead of displacement of the center of gravity. In fact, the binding with the surroundings determines the natural frequency, that is, the number of oscillations per second that the system makes when it is brought out of equilibrium and left to itself afterwards.

It is the natural frequency that determines, among other things, what is measured. This will be illustrated by a few extreme cases (a, b, c), illustrations which, unfortunately, cannot be made entirely without mathematics.

The differential equation of a "swing" loaded with a patient is:

$$M\frac{d^2x}{dt^2} + \beta\frac{dx}{dt} + Dx = m\frac{d^2y}{dt^2}, \qquad (2)$$

in which x is the displacement, $\frac{dx}{dt}$ the velocity, $\frac{d^2x}{dt^2}$ the acceleration, and M the mass of patient and swing together. $\beta\frac{dx}{dt}$ is the frictional force (caused by a damping, applied purposely), and Dx is the restoring force driving the swing to its equilibrium position; m is the mass and y the displacement of the center of gravity of the blood ejected by the heart, so $m\frac{d^2y}{dt^2}$ is the internal reaction force of that blood on the body.

(a). If there is a strong binding D of the system with its surroundings (high natural frequency) then equation (2) is reduced to:

$$Dx = m\frac{d^2y}{dt^2}. \qquad (3)$$

So the recorded deviation x gives a picture of the internal forces.

(b). If the binding to the surroundings is weak (low natural frequency) then equation (2) becomes:

$$M\frac{d^2x}{dt^2} = m\frac{d^2y}{dt^2}. \qquad (4)$$

From this it follows that the recorded displacement x is proportional to the displacements y occurring within the system: $x = my/M$.

(c). If the system is heavily damped and weakly bound to the surroundings, then equation (2) becomes:

$$\beta \frac{dx}{dt} = m \frac{d^2y}{dt^2} \text{ and } x = \frac{m}{\beta} \frac{dy}{dt} \qquad (5)$$

So the measured displacement is proportional to the velocity $\frac{dy}{dt}$ with which the center of gravity of the ejected blood is displaced as a result of the internal forces.

Starr and associates[10] have made the binding of their system (that is, patient and bed) to the surroundings so strong that the natural frequency is about 10 c./sec., while others (Brown[2] and Brown and Pearson[3]) go as far as 15 c./sec., case (a). So the frequency of the ballistocardiograph is high with respect to the frequency of the heart (1 c./sec.). These authors consequently measure forces (high-frequency ballistocardiography).

Nickerson and Curtis[9] use a much weaker binding to the surroundings. The natural frequency is about 1 c./sec. This binding is too weak for measuring forces. It is still too strong, however, for the measuring of displacement; for the frequency is neither high nor low with respect to the frequency of the heart. As the damping in their system is not much more than critical (this case would be c) it is not quite clear what, exactly, is recorded.

The natural frequency of our swing is even lower than in Nickerson and Curtis' method, namely with or without loading 0.3 c./sec. (case b). Consequently we measure, with a reasonable approximation, the displacement of the center of gravity of the blood, resulting from the forces (low-frequency ballistocardiography). This has been applied only by others, as far as we know, many years ago (Gordon[5], Henderson[7]). As the high-frequency ballistocardiograph measures forces and the low-frequency one displacement, the curve recorded by the first type of ballistocardiograph will be the second derivative of the curve recorded by the second type. Conversely, the twice integrated curve of the high-frequency ballistocardiograph is the curve of the low-frequency ballistocardiograph.*

If we make records that reproduce the displacement of the center of gravity (case b), the velocity of this displacement (case c), or the internal forces (case a), it is, in general, incorrect to give the same names to the peaks of the different curves. For, as the example in Fig. 1 shows, in the different cases the peaks may appear not only on quite different points of time, but their meaning and their number also may be quite different.

*When integrating the high-frequency ballistocardiogram it should be borne in mind that, before each integration, the base line of the curve has to be chosen in such a way that the area between the curve and the base line on the positive side for one complete heart beat is equal to the area on the negative side.

It has been stated that if the movement of the system caused by the internal forces is to be exactly measured, this system should not be bound to the surroundings. The low-frequency ballistocardiograph is not without binding. (The natural frequency is after all 0.3 c./sec., instead of 0 c./sec.) The consequence is that the lowest frequencies which may occur in the movement of the blood are partly or entirely eliminated. All higher frequencies, however, are completely represented (see the frequency characteristic: Fig. 2). When we compare this with the frequency characteristic of a high-frequency ballistocardiograph, it appears that the low frequencies entirely or partly disappear into a larger range than is the case with the low-frequency ballistocardiograph. The strong binding of the high-frequency ballistocardiograph to the surroundings is the reason why it does not react to these low frequencies. At high frequencies another decrease occurs (Fig. 2). At these frequencies the tissue of the patient acts as a damping.

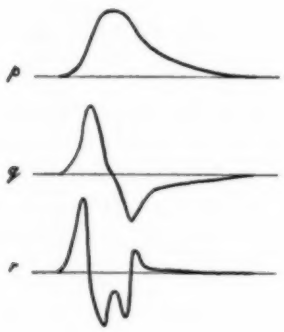

Fig. 1.

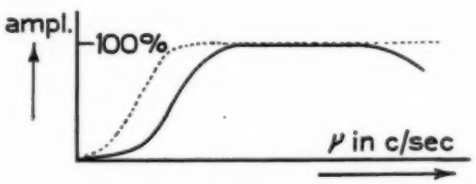

Fig. 2.

Fig. 1.—A curve chosen arbitrarily with its first and second derivative. p = coordinate; q = velocity; r = acceleration (force).

Fig. 2.—Frequency characteristics of a high-frequency (solid line) and a low-frequency (broken) ballistocardiograph (schematic).

It is clear that the difference in the frequency characteristics, as regards the low frequencies, is important when attention is paid to the respiration frequency (about 0.3 c./sec.). With the high-frequency ballistocardiograph this frequency is hardly represented, whereas it is clearly shown by the low-frequency one. For this reason it is necessary that the patient, during the recording with the low-frequency ballistocardiograph, holds his breath or that the influence of respiration is eliminated in some other way.

It has already been pointed out that the high-frequency ballistocardiograph measures forces, and the low-frequency one measures displacements. If these two types of ballistocardiograph were capable of measuring entirely correctly, they would be equal in value, because the one curve could be obtained by a mathematical operation from the other.

The curves of the high-frequency ballistocardiograph have a great uncertainty on account of the patient's movement with respect to the bed. The high-frequency ballistocardiograph is strongly bound to the surroundings, while at the same time, it weighs in the order of 70 kg. The low-frequency one has a very weak binding and weighs about 5 kg. In consequence of these two differences, the patient on the high-frequency table is far less firmly connected to it than on the low-frequency swing. With the high-frequency ballistocardiograph the binding of the patient to the bed is hard to oversee. So with the low-frequency ballistocardiograph we know more precisely what is measured than with the high-frequency ballistocardiograph.

Perhaps the simplicity of the curves obtained with the low-frequency ballistocardiograph is another advantage over the curves obtained with the high-frequency one.

Furthermore low-frequency ballistocardiography is simpler, and the displacements of the swing are greater; hence, the necessary amplification is smaller.

CLOSER EXAMINATION OF THE LOW-FREQUENCY BALLISTOCARDIOGRAPH

Starr and associates[10] do not damp their ballistocardiograph on purpose. Damping our swing has turned out to be a necessity. Not damping it would make an accurate recording impossible on account of oscillations performed by the swing after all kinds of disturbances. From the following calculations it will appear that the recorded curve has been distorted more according as the damping is heavier. The latter therefore should be as weak as admissible. From experiments it became clear that good records could still be made when the swing "overshoots" to 25 per cent. The swing after a disturbance will then do some oscillations in its natural frequency. This damping is strong enough to prevent these oscillations from lasting too long. As will be described further on, this "overshooting" can be regulated by adjusting the damping.

Any periodic phenomenon can be thought of as having been built up from a number of sinusoïds, namely, of a first harmonic having the frequency of the phenomenon and the higher harmonics belonging to it. The damping shifts each sinusoïd in time (phase shift) and, moreover, changes its amplitude. The changes are dependent on the frequency of the sinusoïd in question (so the phase shift and change in amplitude of the first harmonic and a higher harmonic are different). The degree of damping determines how great are the phase shift and change in amplitude of every frequency. The weaker the damping, the smaller the distortion of the ballistocardiogram (Fig. 5).

In order to calculate this distortion we must know β. The latter can be found from the differential equation by determining the relation between damping and "overshooting." If the swing is less than critically damped, then, when displaced from its equilibrium position E (Fig. 3) and released without initial velocity, it oscillates about the latter with decreasing amplitude.

The ratio x/x_0 (Fig. 3) of the amplitudes in two consecutive inversion points is called the overshooting.

The relation between damping and overshooting x/x_0 we find from the differential Equation (2):

$$\frac{x}{x_0} = e^{-\frac{\pi}{\sqrt{1/\delta^2 - 1}}} \tag{6}$$

In this equation δ is the ratio of the damping β to the critical damping (Fig. 4).

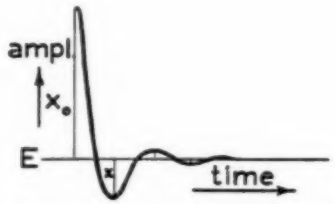

Fig. 3.—The curve written by a swing, damped periodically (overshooting 25 per cent).

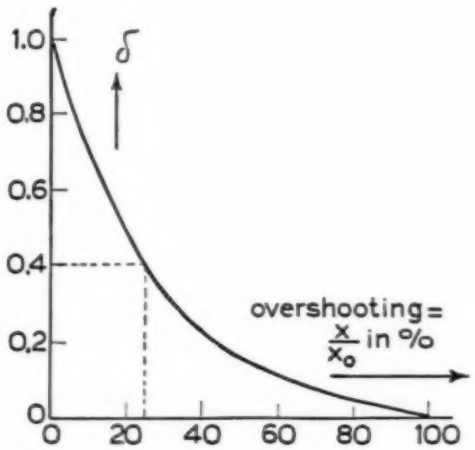

Fig. 4.—The relation between damping and overshooting.

For the phase shift φ we find

$$\operatorname{tg} \varphi = \frac{2\delta\nu_0\nu}{\nu_0^2 - \nu^2} \tag{7}$$

in which ν_0 is the natural frequency of the loaded swing and ν is the frequency of the internal force.

From the differential equation we find also the amplitude

$$x = \frac{m}{M} \frac{\nu_0}{\sqrt{\left(1 - \frac{\nu_0^2}{\nu^2}\right)^2 + 4\delta^2 \frac{\nu_0^2}{\nu^2}}} \tag{8}$$

The phase shift as well as the amplitude can now be expressed numerically, as δ can be calculated from the measured overshooting. From Fig. 4 it appears that with an overshooting of 25 per cent (the one usually applied by us) $\delta = 0.4$. The natural frequency of the loaded swing (ν_0) is 0.3 c./sec. The phase shift and the amplitude as functions of the frequency (ν) of the internal force are graphically represented in Fig. 5. In the same figure, the phase and amplitude characteristics obtained with other degrees of damping also have been drawn. It shows immediately that with the weaker damping the phase shift will be smaller. With stronger damping, however, the amplitude characteristics will be more favorable. As a compromise we chose a damping with 25 per cent overshooting. It is clear that with this overshooting very little distortion occurs in frequencies from which our curve has been built up.

If no damping were used there would be according to equation (7) no phase shift, but according to equation (8), however, there is change in amplitude.

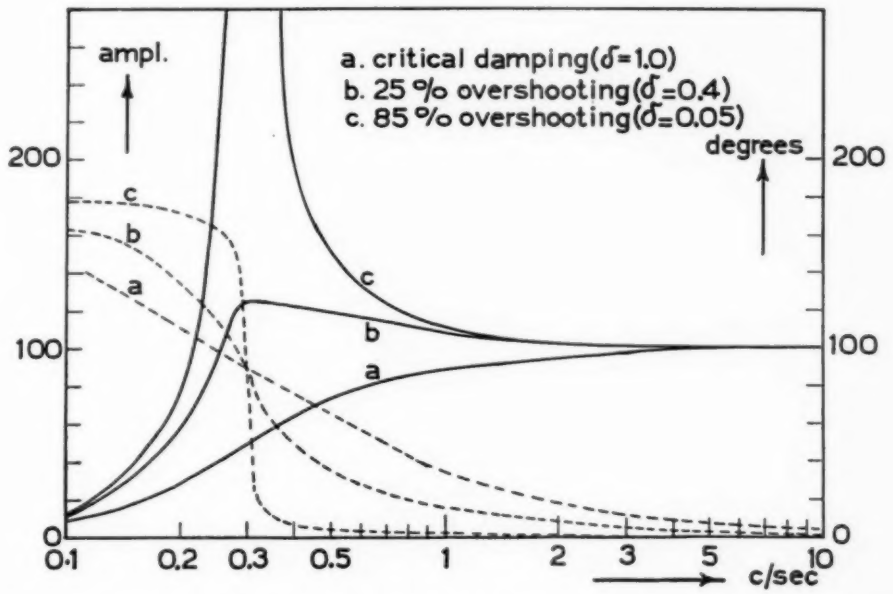

Fig. 5.—Frequency characteristics (solid line) and phase characteristics (broken) of the low-frequency ballistocardiograph with different dampings.

THE RELATION BETWEEN DISPLACEMENT OF CENTER OF GRAVITY AND THE DISTENSIBILITY OF THE BLOOD VESSELS

With every contraction of the left ventricle blood is pushed into the aorta. The latter is temporarily distended by it. This distention starts at the heart, goes on to the periphery, and is damped out. When considering some small part of an artery we find that during distention there is more blood in it than when the distention has passed. This distention goes along the artery and acts as if an extra mass were moving along the artery with the velocity of the pulse wave.

This is true for the aorta and for all other arteries. So in consequence of the contraction of the two ventricles and the distensibility of the arteries, a periodic mass displacement occurs in the body and hence "displacement of the center of gravity."

If the patient is laid on a low-frequency ballistocardiograph, then, because the common center of gravity keeps the same position, the movement of the whole body, followed more or less by the swing, can be recorded. (Fig. 7 is an example.)

We have seen that the mass displacement on account of the pulse wave gives a displacement to the body in the opposite direction. A constant filling of a blood vessel would not give the swing a displacement even when the blood is moving, as no change in mass distribution in the blood vessel would occur.

The pulse wave is found mainly in the aorta and the pulmonary artery as they distend most, and to a lesser degree also in their large branches. As there is a venous pulse the veins also contribute, but how much? Also, the displacement of tissue on account of the pulse wave and the displacement of the heart cause mass displacement.

Every mass displacement along each blood vessel in which this phenomenon occurs causes an opposite displacement of the swing. The sum of the different effects is measured. That is the reason why analyzing the curve is difficult. From this it follows that the form of the curve is determined for the greater part by the anatomical structure of the patient.

THE INSTRUMENT

Our ballistocardiograph consists of a bed (200 by 80 cm.) suspended from the ceiling on four wire ropes of equal length (300 cm.) and 12 mm.² in diameter. The wire ropes have been fixed to points of suspension in such a way as to run parallel. The advantage of parallel ropes is that the bed always keeps the same position regardless of the place the patient occupies on it.

The bed consists of a steel tube bent rectangularly. In this frame a piece of canvas has been stretched. At the foot-end there is a vertical plate enabling the patient's feet to make firm contact and securing a better fixation of the swing to the patient. An adjustable damping device is located at the head-end and foot-end. The damping is supplied by making horizontal aluminum plates of 14 by 8 cm. move in shallow boxes filled with treacle. These plates are strongly attached to the frame, while the distance, between each plate and the bottom of the box belonging to it, is adjusted by moving the box containing treacle vertically. A stronger damping can be obtained by decreasing the distance between plate and bottom of the box. In that case, with the same velocity, a greater gradient in velocity is caused in the treacle between plate and bottom and, therefore, a stronger damping. Conversely the damping can be made weaker by increasing the distance between plate and bottom.

The total mass of the swing, the attached footplate, and the damping device is 5 kg. The damping is adjusted in such a way that the swing with patient overshoots 25 per cent ($\delta = 0.4$) and then the movement in the longitudinal axis

of the patient is recorded.* A weaker damping gives too much waving in the curves, while on the other hand, the damping should be kept as light as admissible to make the distortion as small as possible. With every patient the damping has to be adjusted anew, because there will be a difference in the mass of this patient plus swing, thus, in the strain of the wire ropes and in the bending of the swing, and hence, in the thickness of the layer of treacle.

In order to record the movement of the ballistocardiograph we have used until now two methods (out of many possibilities) which we shall call (a) the mirror method and (b) the phototube method.

(*a*) *The Mirror Method.*—A small brass plate is soldered to a vertical steel wire which is stretched between two fixed points. On this plate a little mirror is fixed, and in the plate a number of holes are drilled in a horizontal line. If the brass plate is first turned in such a way around the wire as an axis of rotation, so that a thread now connecting swing and wing is taut, then the to-and-fro movement of the swing will cause the mirror to turn round. (The directive force, caused by the steel wire and acting on the brass plate, is strong enough to record even the highest frequencies that are of interest.) The rotation of the mirror and with it the swing movement can be recorded; the mirror is illuminated from a fixed direction by a slitlike source. The image of the slit, formed by the reflected lightbeam is received by a film moving perpendicularly to the to-and-fro movement of the image of the slit. The amplification can be regulated by making use of different holes drilled in the brass plate. It is equal to twice the distance torsion wire-film over the distance torsion wire-hole in the plate. For testing purposes the swing may be given a known displacement and the appertaining deflection of the light spot recorded. The usual amplification is about 200 times.

With this method the distortion of the curve is negligible and the apparatus is very simple.

(*b*) *The Phototube Method.*—A circuit is formed, consisting of a phototube, a voltage supply, and a resistance. If light is made to fall on the phototube, a current will start in the circuit. Between the terminals of the resistance a voltage will arise that is proportional to the amount of incident light. If the amount of light incident on the phototube is variable, then the current in the circuit will vary with it, and hence the voltage over the resistance. The optics belonging to the phototube are schematically represented in Fig. 6.

The filament of the illuminating lamp is projected on the phototube, so as to eliminate the influence of possible differences in sensitivity over the surface of the phototube. If, in fact, a part of the lightbeam is screened off in the place of the arrow in Fig. 6, a complete image of the filament still is obtained, but this image is more feebly illuminated over the entire surface. Moreover, with this optical arrangement the lightbeam is homogeneous in the neighborhood of the arrow.

A screen is attached to the swing. When the swing is in zero position, it has its edge in about the middle of the lightbeam, at the place indicated by the arrow

*The device used also enables recording the lateral movement.

in Fig. 6. In this place we have the image of the first lens opening, a square diaphragm (size 26 mm.) giving a square image. (The image is one-fourth the size of the object in order to obtain a greater sensitivity). When the swing is moving, then alternatively more and less light is transmitted to the phototube. In this way variations of voltage on the resistance in the phototube circuit are obtained, which, connected with an electrocardiograph, make the latter write a curve representing the movement of the swing.*

As existing types of electrocardiographs with a sufficiently long R-C time can be made use of, this method of recording is directly suitable for application in hospitals. By means of suitable apparatus ballistocardiograms can be made synchronous with electrocardiograms and phonocardiograms.

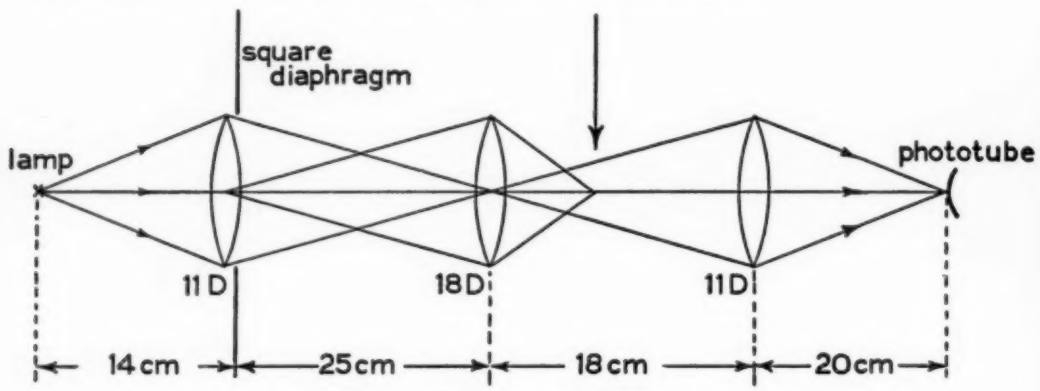

Fig. 6.—The optics of the phototube.

The homogeneity of the lightbeam has been examined. For this purpose the phototube was replaced by a thermopile, connected with a galvanometer. A screen (in the place of the arrow in Fig. 6) was moved through the beam with equal steps. At every position of the screen the galvanometer was read. From this it appeared that the middle 4 mm. out of the total width (7 mm.) were homogeneous within 1.5 per cent. This not only holds for the place of the arrow but also for the places 2 cm. in the direction of lamp and phototube, respectively. So on adjusting the screen it is not necessary to take care that the screen is exactly in the middle of the lightbeam and in the place of the arrow.

The sensitivity of the entire design (i.e., inclusive of the amplification of the electrocardiograph) can be calibrated by fixing a thin wire (0.1 mm. in diameter) to the screen in such a way that it comes into the beam parallel to the vertical edge of the screen. (The diameter of the wire has been made this small, because the movement of the ballistocardiograph with respect to the heartbeat is not more than about 0.1 mm.) By pressing a photoshutter the wire will suddenly spring out of the lightbeam, making the electrocardiograph record a deflection that corresponds with the swing's movement over a fixed distance, namely, the thickness of the wire. In this way, the sensitivity can be calibrated during the recording.

*An electrocardiograph does not react on the constant input voltage caused by that part of the lightbeam which is not screened off at any moment by the movement of the swing.

RESULTS OF THIS METHOD

Figures 7 and 8 give the curves of different, normal subjects holding their breaths; H is the headward direction of the swing-movement; B, C, D . . . are the names of the peaks. These curves represent the recording of the movement of the swing and not the movement of the subject; that is, in using the mirror method the thread causing the mirror to move is not attached to the subject itself, but to the swing. With the phototube method the screen is fixed also to the swing. Recording directly from the subject is preferable, in principle, to recording from the swing, because the swing does not follow accurately the movement of the subject lying on it. It appeared, however, that in general the patient cannot lie sufficiently still to permit obtaining a record directly

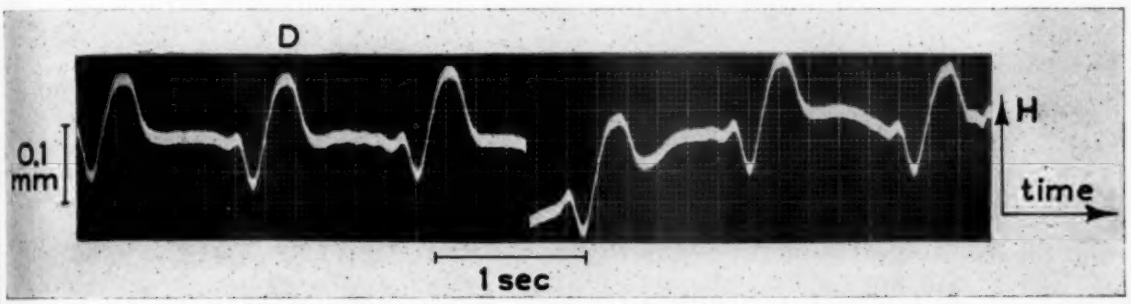

Fig. 7.—Ballistocardiogram with calibration of the sensitivity, recorded by an electrocardiograph.

from him. Hence records were obtained of the movement of the swing. So the error arising from the fact that the swing does not follow the body exactly is included in our curves. In order to determine how great this error is, synchronous records were taken of the movement of the swing with respect to the surroundings and of the swing with respect to the subject. In order

Fig. 8.—A ballistocardiogram synchronous with the movement of the swing, with respect to the patient, recorded by the mirror method.

to record both movements, a second mirror is fixed to the swing. During this recording the subject had a helmet on his head (the band round the chin as tight as possible). In this helmet a hook was soldered to which can be attached the thread transmitting the movement of the swing with respect to the subject to the brass plate of the mirror system. By the mirror method this movement is recorded on the same film as the common movement of the swing with respect to

the surroundings. With the original, rather heavy, swing (12 kg.) the relative movement (that is, swing with respect to subject) may be as much as 30 per cent of the movement of the swing. If the swing is made lighter, it will be able to follow the subject more accurately; therefore, the mass of the swing has been made as small as possible (5 kg.). By these means the relative movement could be expected to be $5/12 \times 30$ per cent $= 12$ per cent. If, moreover, the swing is

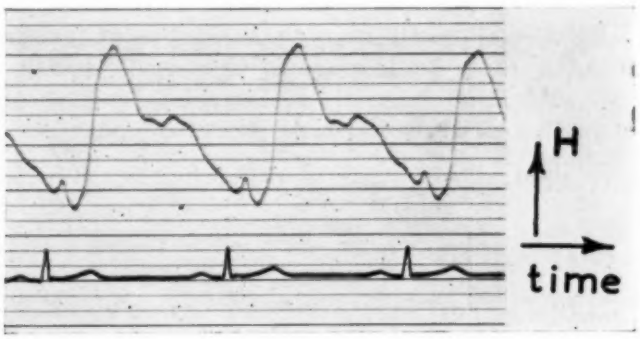

Fig. 9.—A ballistocardiogram synchronous with electrocardiogram.

better attached to the subject, then the relative movement for this reason will be less. The footboard mentioned earlier with which the patient's feet are in firm contact has been fixed for this purpose. Moreover, the damping has to be as weak as possible. The relative movement thus is reduced to about 6 per cent. Figure 8 shows a normal ballistocardiogram and the relative motion belonging to it, synchronously recorded by the mirror method.

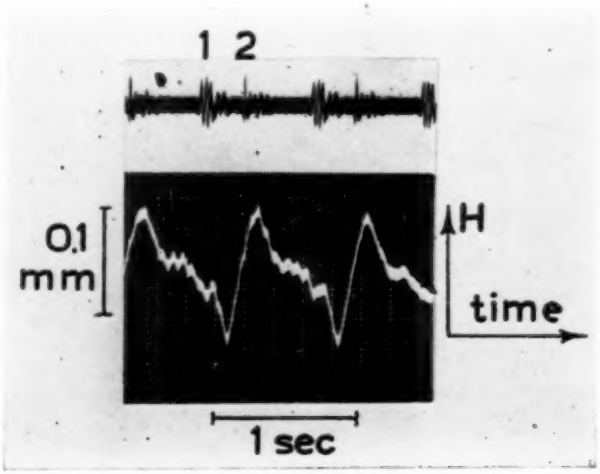

Fig. 10.—Synchroncus curve of a ballistocardiogram and phonocardiogram.

Examples of synchronous records of ballistocardiogram with electrocardiogram or phonocardiogram are reproduced in Figs. 9 and 10. For instance these records can be made use of to settle the question whether the little peak (B) that is to be seen at the beginning of the heart beats in many ballistocardiograms (Figs. 7 and 8) appears at the beginning or at the end of a heart beat.

SUMMARY

A ballistocardiograph has been constructed which is bound so weakly to the surroundings that the displacement of the center of gravity of the blood, caused by the action of the heart, can be measured.

Damping the ballistocardiograph appeared to be necessary. The influence of the binding to the surroundings and of the damping has been examined.

Records can be made by an electrocardiograph. During the recording the breath is held.

The obtained curve may be compared with others, generated by the heart action.

High-, middle-, and low-frequency ballistocardiographs have been compared theoretically.

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ESOPHAGEAL PRESSURE PULSE PATTERNS (ESOPHAGEAL PIEZOCARDIOGRAM)

III. Mitral Insufficiency

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THE evaluation of the significance of an apical systolic murmur is one of the particularly perplexing problems in clinical cardiology. The positive identification of minimal mitral insufficiency on the basis of physical signs and roentgenogram evidence is frequently difficult and depends to a large extent upon the subjective judgments of the observer. Difficult, too, is the estimation of the degree of valvular damage sustained during a bout of acute rheumatic fever.

A comparison was therefore made between the esophageal pressure pulse patterns (piezocardiogram) of: (1) patients with clinically evident mitral insufficiency; (2) patients with or recovering from acute rheumatic fever, and (3) normal individuals.

These esophageal pressure pulse patterns are formed by the pulsation of the left atrium which, as it undergoes changes in shape and volume, results in a regularly fluctuating compression of the esophagus. Recordings of these esophageal pulsations are obtained by means of a balloon inserted into the esophagus and positioned fluoroscopically at the level of the left atrium.

It has previously been shown that the esophageal pressure pulse patterns so recorded are very close replicas, qualitatively, of the pressure pulse patterns of the left atrium.[1,2] The contours of the curves obtained from normal individuals and those of patients with various types of rheumatic involvement of the mitral valve have also been reported.[3]

The term esophageal piezocardiogram has been used to describe these recordings.

METHODS

The previous investigations, rational for, and the technique of obtaining, satisfactory esophageal piezocardiograms have been described in detail previously. The technique consists in passing into the esophagus a specially constructed tube

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of polyethylene with an attached inflatable rubber balloon. The balloon is positioned under fluoroscopic control at the left atrium and is then inflated with water. The proximal end of the tube is attached to an electromanometer for the recording of the fluctuations of pressure within the system. This in turn leads to a direct writing Sanborn polyviso cardiette where the actual graph is recorded along with a simultaneous electrocardiogram and phonocardiogram. The patient is supine and is usually kept apneic during the recording period. Several tracings are usually taken to explore the entire zone of esophageal-left atrial contiguity. Frequent fluoroscopic checks are made to be sure that the position of the balloon has not shifted.

The patients for this study were selected from the wards and private services of The Jewish Hospital of Brooklyn. Normal individuals were those without observable valvular heart disease either on physical or fluoroscopic examination or by history. One group of six patients with clinically evident mitral insufficiency was selected on the basis of (1) a loud apical systolic murmur (Grade 3 or more), (2) absence of apical diastolic murmur or mitral click, (3) fluoroscopic evidence of left ventricular enlargement and, in several, the presence of an electrocardiographic pattern of left ventricular hypertrophy. All showed evidence of left atrial enlargement. Basilar systolic and diastolic murmurs were present in some of these patients. A second group consisted of four children who were either in the active or convalescent phase of their first attack of acute rheumatic fever.

RESULTS

The Normal Piezocardiogram.—The tracings obtained in four normal individuals are shown in Fig. 1. The following characteristics are observed: (1) A rise in pressure, which represents atrial systole, begins 0.04 to 0.06 second after the onset of the P wave of the electrocardiogram. The average height of this wave from highest to lowest point is 3.5 mm. Hg with a range of 0 to 5 mm. Hg. (2) A series of rapid oscillations follows next. These occur during the first heart sound and probably represent its low frequency components. Their onset signals the closure of the mitral valve and the onset of ventricular systole. (3) During ventricular systole the trend of the curve is downward in the early phase and rising in the late phases. The fall in atrial pressure which accompanies "the descent of the base" is occasionally marked as is shown in Fig. 1*B* but more often slight as in Fig. 1*A*. During the remainder of ventricular systole, atrial filling occurs and the curve therefore rises in a gentle slope. This results in a late systolic wave similar to the "V" described in right atrial pressure tracings. The height of this wave varies from 1 to 5 mm. Hg. (4) The curve then falls at the reopening of the mitral valve.

Mitral Insufficiency.—The curves obtained in ten patients with mitral insufficiency are shown in Figs. 2, 3, and 4. Three patterns are apparent.

The first pattern is exemplified by the tracings in Fig. 2. They are characterized by: (1) an accentuated wave of atrial systole measuring an average of 10 mm. Hg from highest to lowest point; (2) a gradually rising wave of pressure which begins its ascent in the early phases of systole, rises progressively,

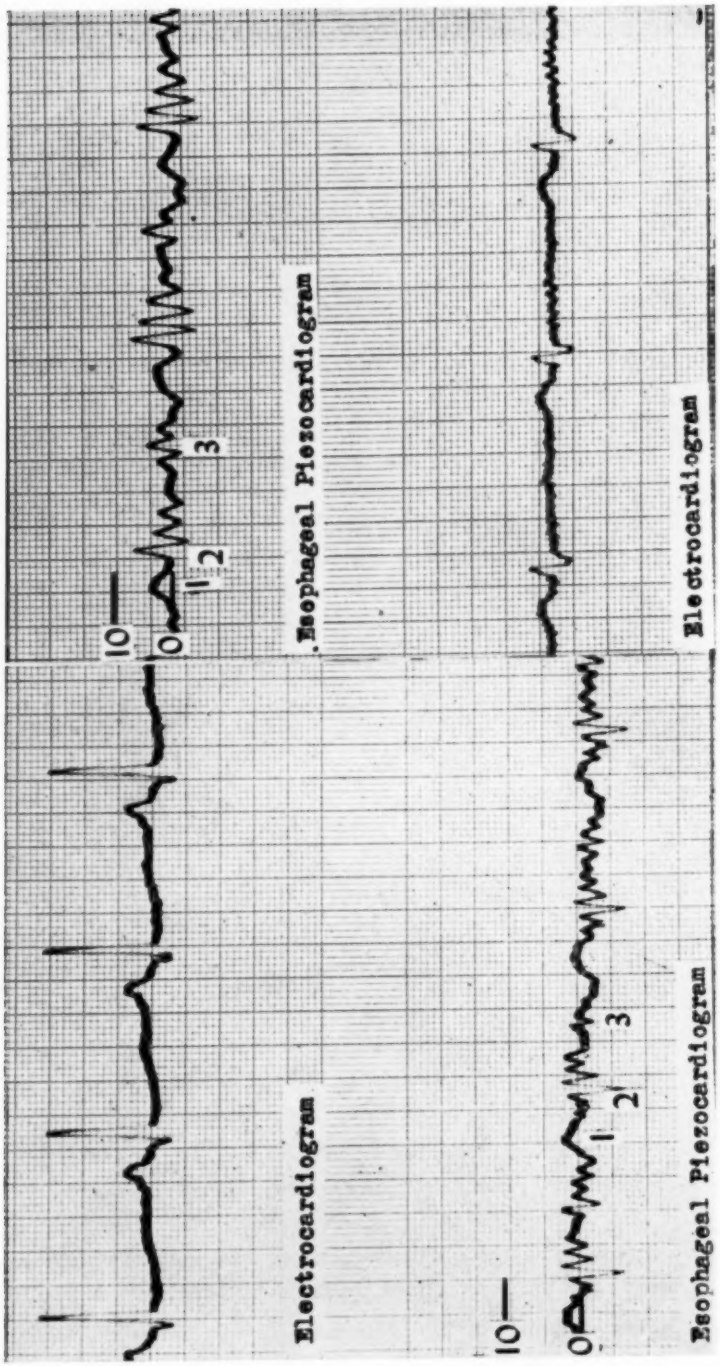

Fig. 1A.—Normal esophageal piezocardiograms. *1* = Atrial systole, *2* = onset of ventricular systole—mitral valve closure, *3* = reopening of the mitral valve.

and reaches a peak just prior to the opening of the mitral valve. The respective heights of these late systolic peaks in each tracing are 6.3, 20.0 and 17.0 mm. Hg. This is measured as the height of the wave peak above the level existing just prior to ventricular systole. The curve then falls sharply.

The tracing in Fig. 2*A* was obtained from a 40-year-old woman with a history of cured subacute bacterial endocarditis. Her heart was not enlarged and only minimal enlargement of the left atrium was observed. A Grade 4 apical systolic murmur was the only audible one. The tracing Fig. 1*B* was obtained from a 26-year-old man who showed evidence of aortic stenosis and mitral insufficiency on physical examination. Cardiac fluoroscopy revealed that there was a slight enlargement of the left ventricle and moderate enlargement of the left atrium.

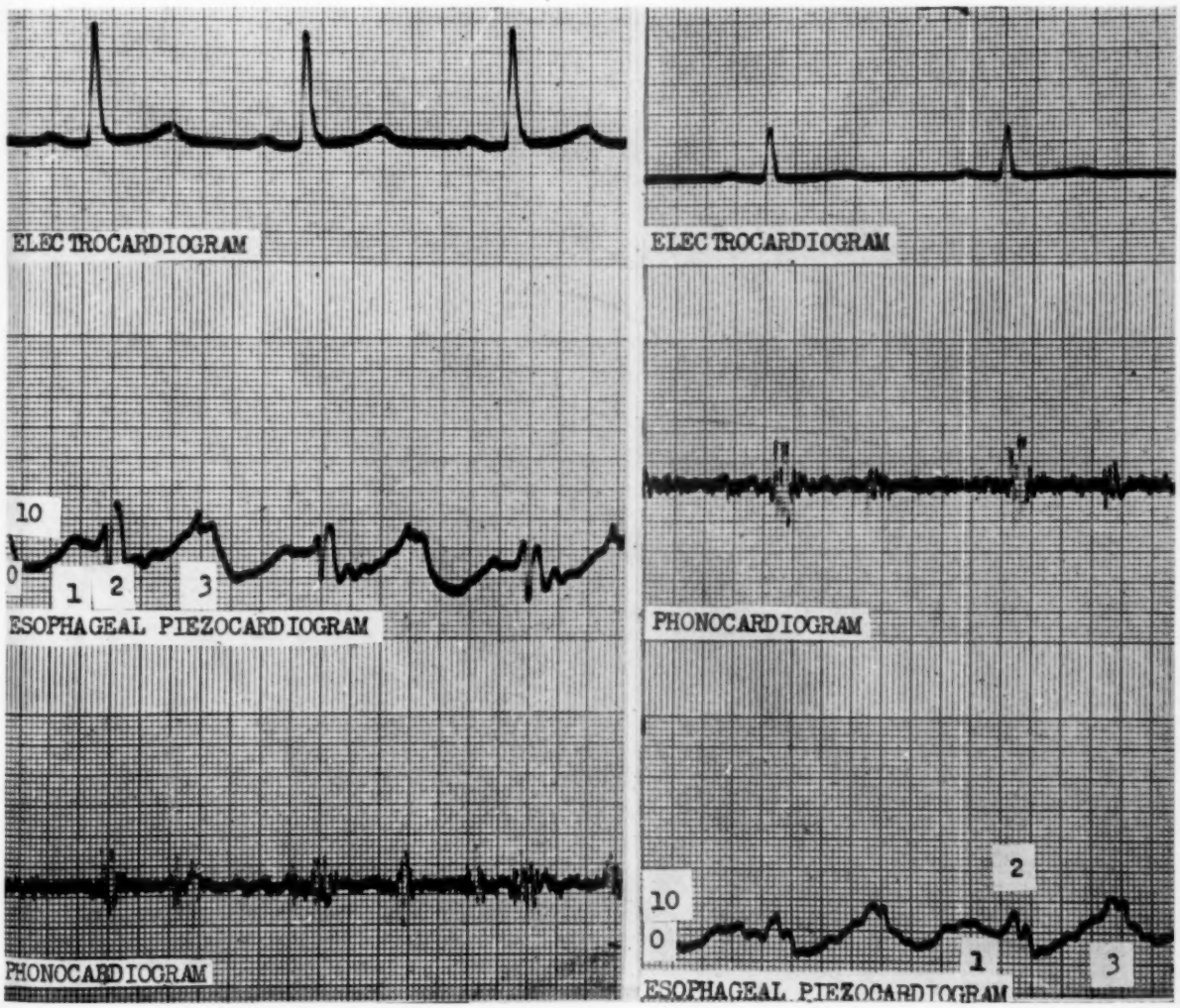

Fig. 1*B*.—Normal esophageal piezocardiograms. *1* = Atrial systole, *2* = onset of ventricular systole—mitral valve closure, *3* = reopening of the mitral valve.

The tracing in Fig. 2*C* was obtained from a 12-year-old girl during an acute episode of rheumatic fever. A systolic murmur of Grade 2 intensity was audible and cardiac fluoroscopy showed minimal cardiac enlargement with no specific chamber enlargement.

The second pattern is seen in the tracings of Fig. 3. These curves are characterized by only slight or no increase in the amplitude of the wave of atrial

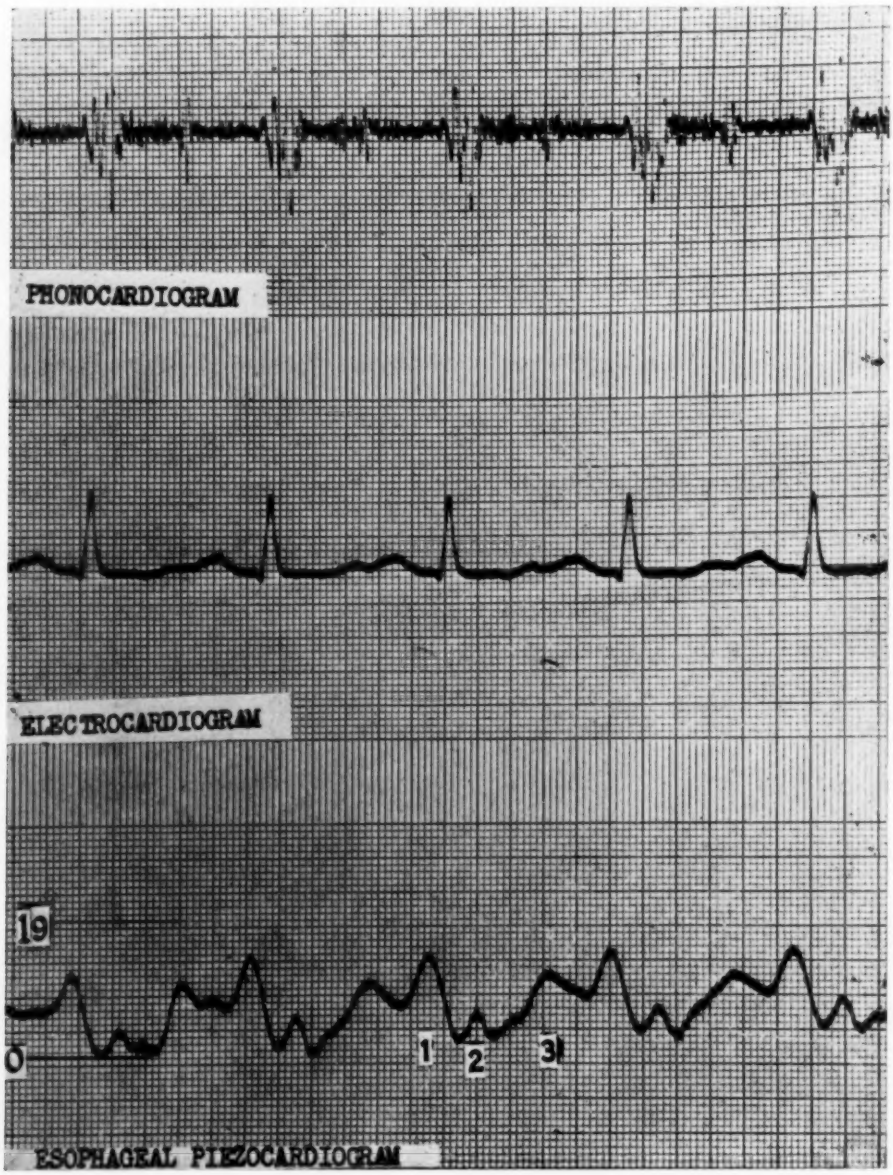

Fig. 2*A*.

Fig. 2.—Mitral insufficiency, Group 1. Note the accentuated wave of atrial systole *1*, and the increased amplitude of the "v" wave *3*.

systole. A rise in atrial pressure during ventricular systole is evident. This pressure wave rises progressively and reaches a peak just prior to the opening of the mitral valve. The heights of these late systolic pressure peaks are, respectively, *A*, 12 mm. Hg; *B*, 13 mm. Hg; *C*, 9 mm. Hg; *D*, 8 mm. Hg; *E*, 13.6 mm. Hg.

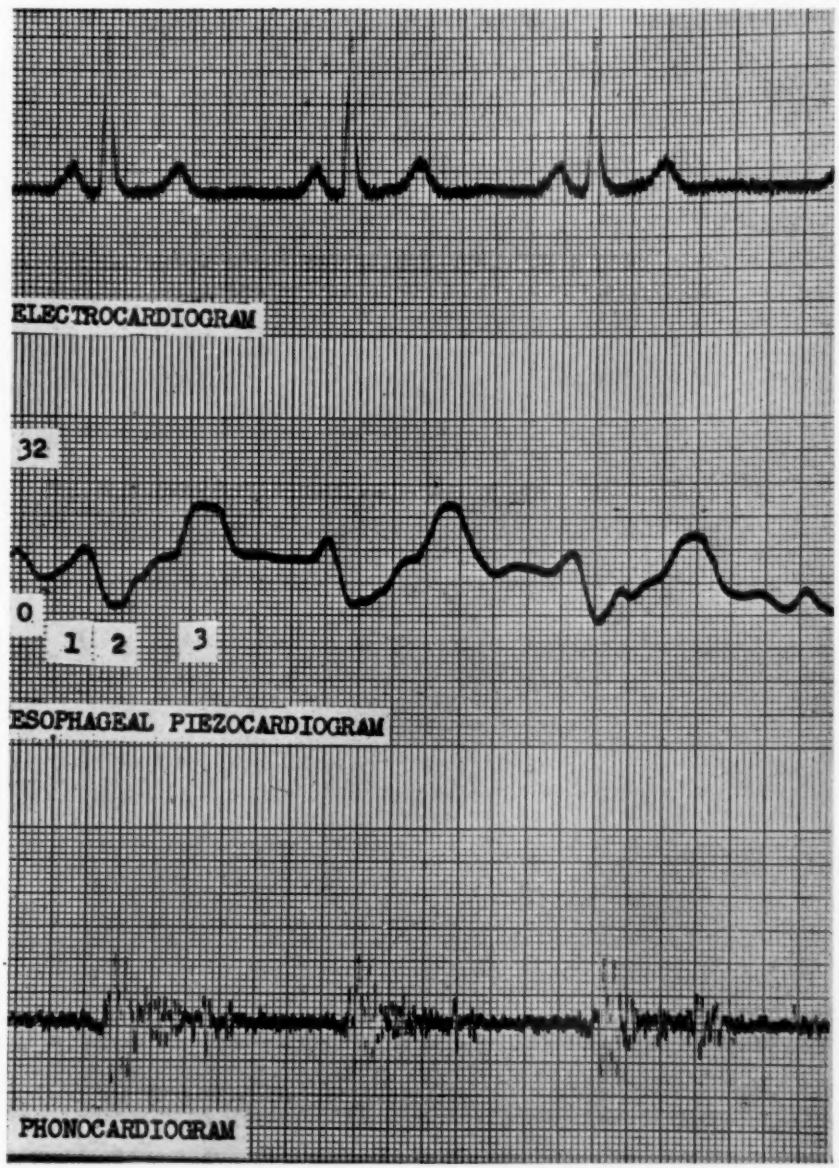

Fig. 2*B*.

The three tracings (Fig. 3*A*, *B* and *C*) were obtained from children during episodes of acute rheumatic fever. None of these children showed fluoroscopic evidence of enlargement of the left atrium, though generalized cardiac dilatation

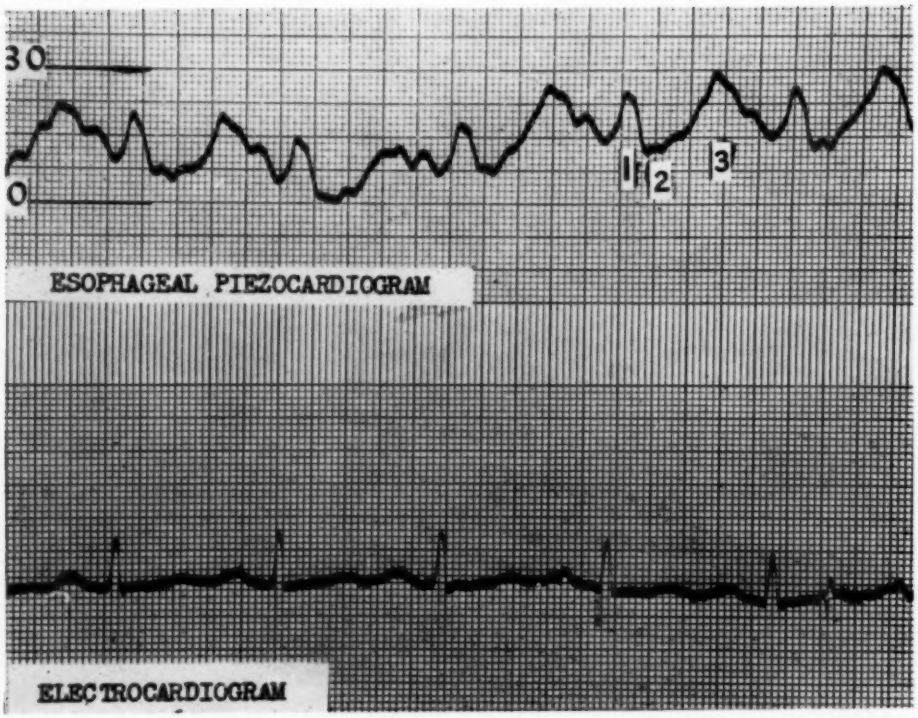

Fig. 2C.—*For legend see p. 88.*

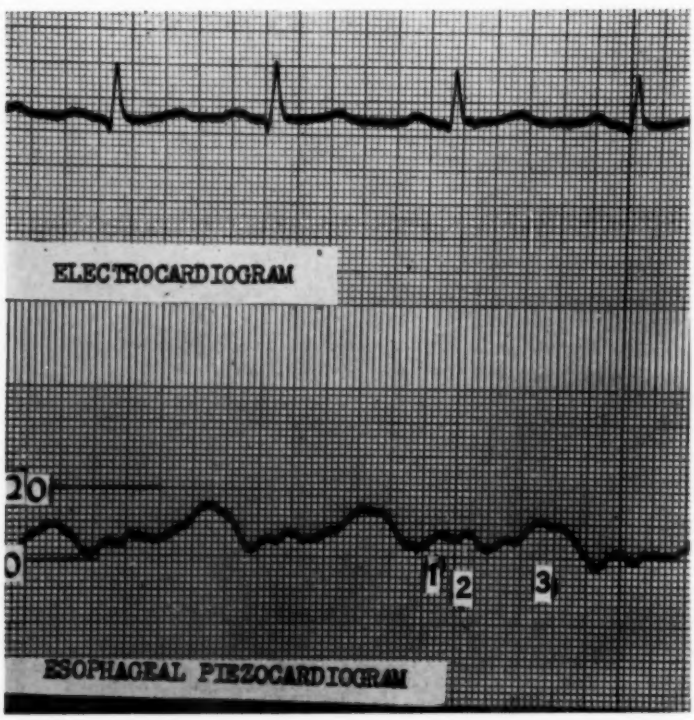

Fig. 3A.

Fig. 3.—Group 2. Note the rise of pressure in the piezocardiogram during the period of ventricular systole (between 2 and 3) which results from ventriculo-atrial regurgitation.

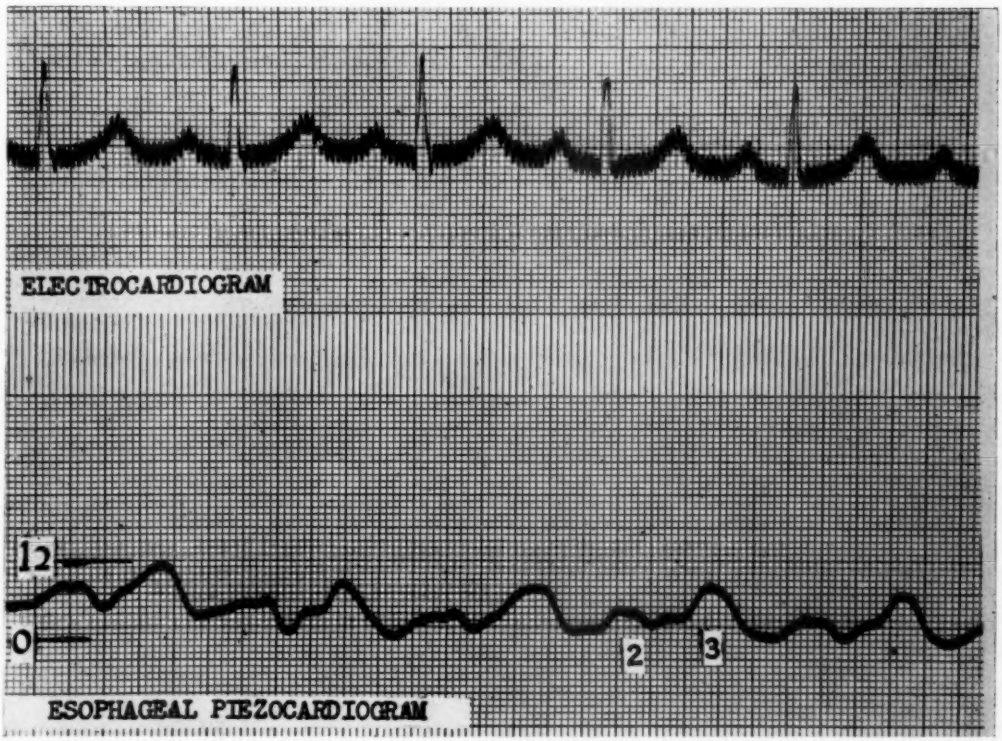
ELECTROCARDIOGRAM
12
0
2
3
ESOPHAGEAL PIEZOCARDIOGRAM

Fig. 3*B*.

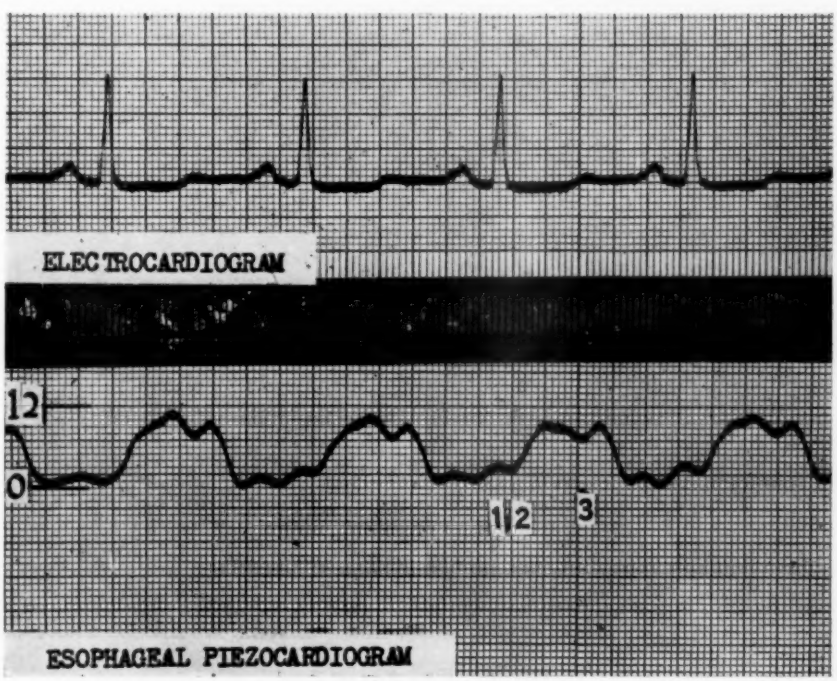
ELECTROCARDIOGRAM
12
0
1 2
3
ESOPHAGEAL PIEZOCARDIOGRAM

Fig. 3*C*.

was present in the first patient, *A*. The patients whose tracings are shown in Fig. 3*D* and *E* were adults with obvious physical and fluoroscopic evidence of rheumatic mitral valvular insufficiency.

The third type of pattern which has been found is shown in Fig. 4*A* and *B*. This pattern shows a feature not seen in the other tracings. In addition, one notes the previously described findings of: (1) An accentuated wave of atrial systole, (2) positive pressure wave during ventricular systole which reaches a peak just prior to the reopening of the mitral valve. This additional feature is

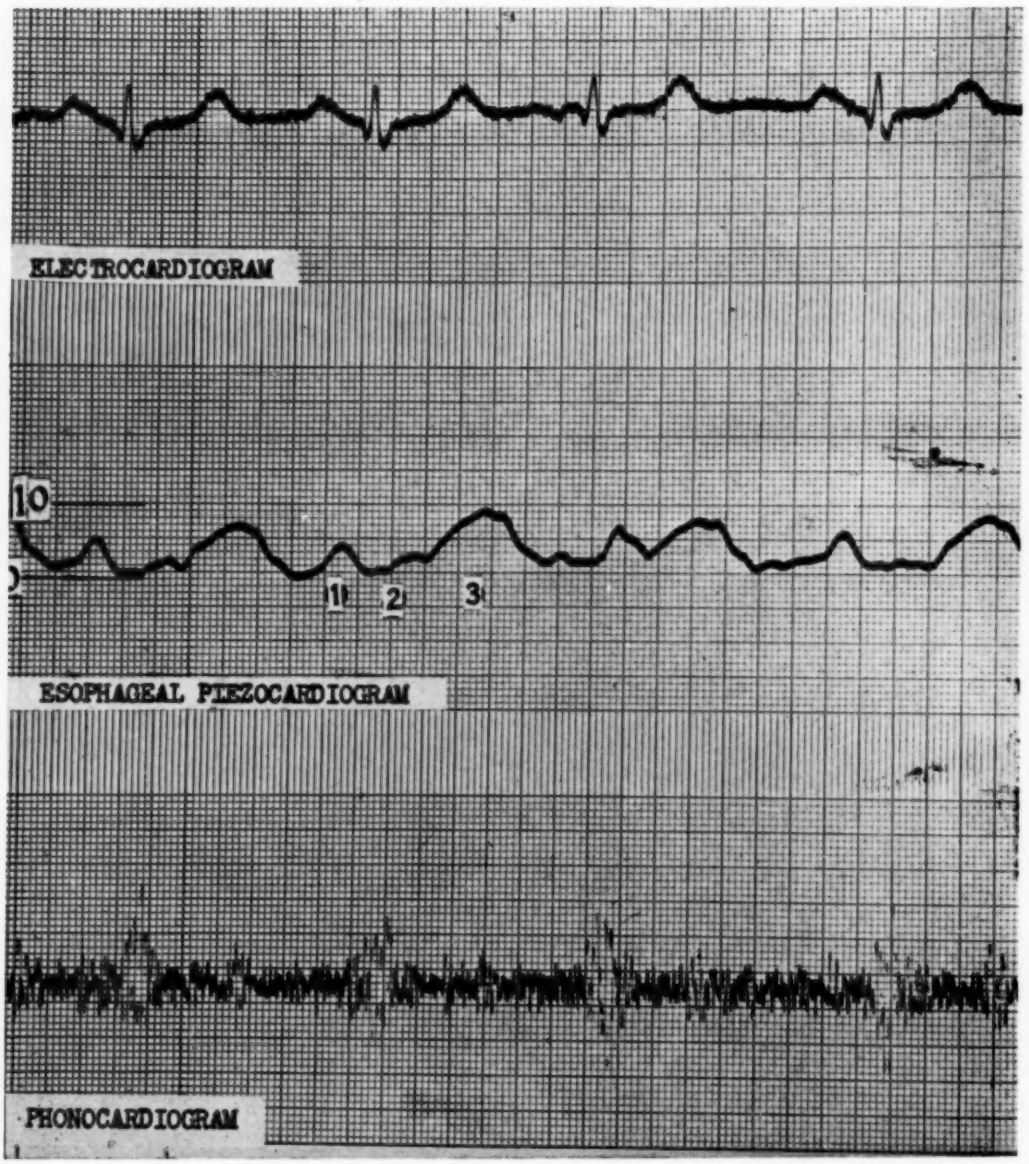

Fig. 3*D*.—*For legend see p. 90.*

the presence of a marked pressure spike at the onset of ventricular systole, coincident with the first heart sound. In Fig. 4*A*, the pressure, following the abrupt early systolic rise does not fall quite to the base line before the marked secondary or regurgitant pressure wave manifests itself. This secondary rise of pressure then carries the curve to a higher peak than that achieved by the early systolic pressure rise. In Fig. 4*A* an interesting sidelight is noted. The last beat shown is a premature contraction, one in which diastolic filling time is reduced resulting presumably in a decrease in left ventricular stroke volume. The piezocardiogram shows an increase in the amplitude of the early systolic spike, and a decrease in the height of the secondary pressure wave or regurgitant wave. This phenomenon has been noted on several occasions. The tracings in Fig. 4*B* are very similar to those of Fig. 4*A*.

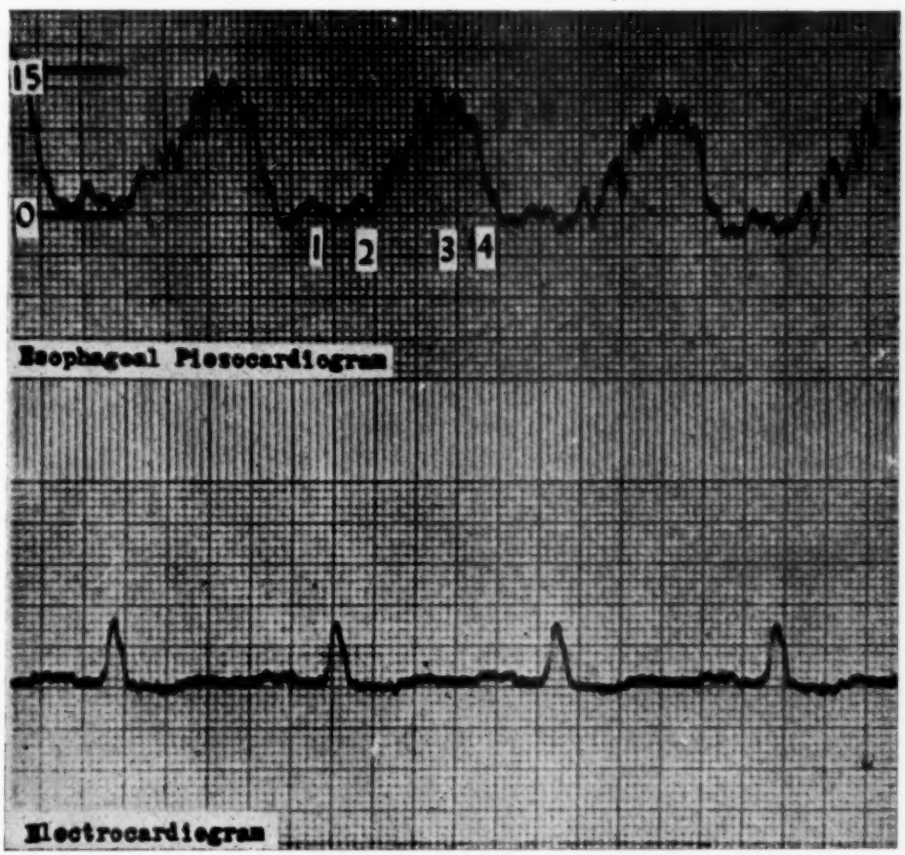

Fig. 3*E*.—*For legend see p. 90.*

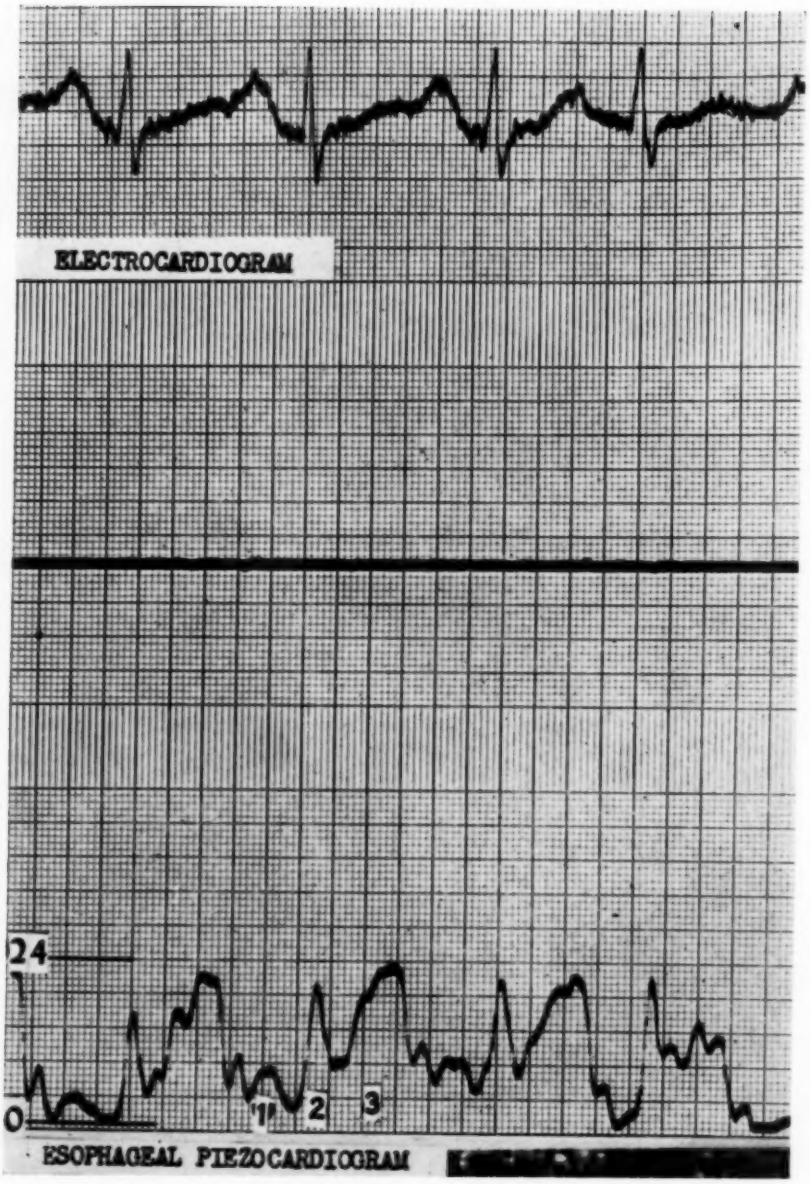

Fig. 4A.

Fig. 4.—Group 3. Note the accentuated wave of atrial systole *1*, the pressure spike at the onset of mitral valve closure *2*, and the secondary rise in pressure attributable to regurgitation *3*.

The pressure during atrial systole is 5 mm. Hg in Fig. 4*A* and 7 mm. Hg in Fig. 4*B*. The height of the secondary or regurgitant wave is 18 mm. Hg in Fig. 4*A* and 16.6 mm. Hg in Fig. 4*B*.

Both patients from whom these tracings were obtained were afflicted with aortic insufficiency in addition to mitral insufficiency. Both were adults whose valvular disease had resulted in considerable enlargement of the left ventricle and left atrium and both showed signs of early heart failure.

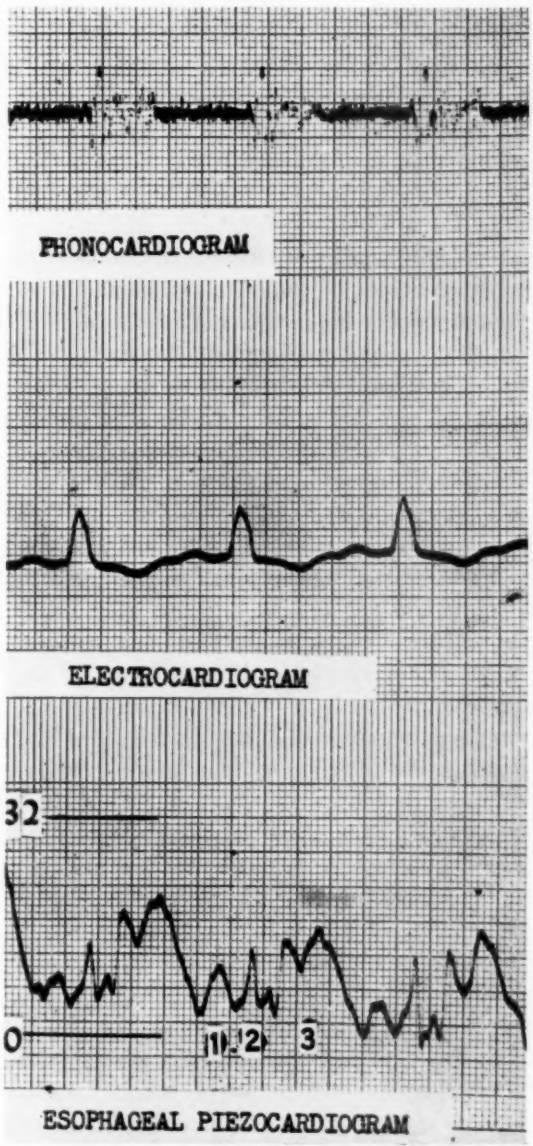

Fig. 4*B*.

DISCUSSION

The evidence for the statement that the esophageal piezocardiograms are accurate qualitative replicas of left atrial pressure pulse patterns has been gathered from studies in animals. This evidence, which has previously been presented in detail, consists in the demonstration in dogs of the similarity between simultaneously recorded piezocardiograms and left atrial pressure pulses obtained following production of mitral insufficiency, mitral stenosis, and congestive failure. Moreover, the esophageal piezocardiographic patterns presented here, obtained from humans, resemble both the tracings found in experimental animals and those tracings reported by other investigators which have been obtained from the left atrium directly during operation on the mitral valve.[4]

Recently, a report has appeared in which esophageal piezocardiographic tracings taken with the technique described by us have been compared with direct left atrial pressure tracings obtained from the same individual. The contours of the two tracings were found to be essentially identical.[5] This work, then, reproduces in humans the original observations which were made in animals. Though this qualitative relationship seems clear, the quantitative relationship between the pressure fluctuations of the left atrium and those of the esophageal piezocardiogram is not known. How this may be modified by the position of the heart in the chest, the phase of respiration, or presence of mediastinal disease, awaits further study. Therefore, any inferences drawn from the amplitudes of the various waves reported here are to be considered as purely empirical observations.

The first feature of these piezocardiographic tracings of mitral insufficiency is the presence of an accentuated wave of atrial systole. This was not uniformly present, but when it was, the appearance suggested that in that particular individual, atrial systole played a substantial role in the emptying of the left auricle and filling of the left ventricle.

The second main feature is the presence of a positive pressure wave occurring during the period of ventricular systole, beginning at or shortly after the first heart sound. This appears to eliminate an initial pressure decline which exists in normal individuals and has been correlated with the "descent of the base." The pressure then continues to mount during ventricular systole and reaches a peak just prior to the reopening of the mitral valve. This is the configuration which is felt to characterize a regurgitant pressure wave. It conforms with the original description by Wiggers[6] of pressure and volume events in experimental mitral insufficiency and has been confirmed by our own unpublished and other observations.[7] Wiggers pointed out that little regurgitation was evident during the isometric contraction phase of ventricular systole, but that regurgitation increased as ventricular ejection proceeded, to reach a peak even after the "reduced ejection" phase had begun. This same character is likewise evident in published tracings obtained from the left atrium in patients with mitral insufficiency at the time of mitral valve operation. It has also been noted in "pulmonary capillary pressure" tracings.[8] This regurgitant wave does not differ greatly in a qualitative way from the normal wave of atrial filling except possibly in the absence of that pressure fall in early systole resulting from "descent of the base."[8] This may

perhaps prove to be useful as a differential point. Quantitatively, the magnitude of this "v" wave is greater than that of the normal wave, though even here some overlapping may occur. In the great majority of cases so far studied, however, the height of this wave above that of the "end diastolic filling" pressure is much greater than that of the normal wave.

There is much question about the third feature seen in some of these piezocardiograms, namely that pressure spike occurring at the onset of ventricular systole. This same early systolic pressure peak has been noted more often with predominant mitral stenosis than with insufficiency. That it is not related to regurgitation is suggested by the observation of Wynn and associates[7] who point out that (in direct atrial tracings from patients with isolated mitral stenosis) this early systolic peak is diminished following a long diastolic filling time and is increased in the presence of a short one. This is the opposite of what would be expected to occur were this the result of regurgitation. Regurgitation should presumably increase with increased ventricular filling and the resulting increased ventriculo-atrial pressure gradient. This observation is supported by our own observations that a premature beat results in an increased height of this early systolic spike and a decrease in the amplitude of the secondary or regurgitant pressure wave.

The relationship between the height of this secondary or regurgitant wave and the magnitude of regurgitation is unknown. This relationship between pressure and volume in the atrium is a complex one as it is determined by the mean tensile strength of the atrial wall at any instant. The contribution to the height of the secondary wave from the pulmonary veins in the form of inflow is another factor which cannot be assessed. Finally, the height of this secondary or regurgitant wave might possibly be augmented by a transmission of the pulmonary artery pulse through the valveless, distended pulmonary vascular system.

It is interesting that some children who had suffered their first attack of rheumatic fever and who showed very little clinical evidence of valvular damage had abnormal piezocardiographic tracings. Only the abnormal tracings have been shown here. Other children who were clinically similar showed entirely normal tracings.

It would appear as though rather distinctive piezocardiographic patterns can be observed in frank mitral insufficiency, which patterns are of diagnostic value. The full range of pattern variability in patients with mitral stenosis and insufficiency has not as yet been ascertained. Moreover, the hemodynamic events and variables which finally result in any one pattern have not been adequately studied. Therefore, since insufficient data are available for purely empirical conclusions and not enough physiologic understanding for reasoned deductions, it is felt that these tracings serve better as a supplement to clinical judgment in the evaluation of patients for operation rather than as a definitive arbiter.

CONCLUSIONS

The esophageal piezocardiograms obtained from normal individuals and from those with mitral insufficiency have been presented. The chief characteristics of these esophageal tracings are very similar to those of direct left atrial pressure pulse curves.

The deviations from the normal curve which result from mitral insufficiency are (1) an accentuation of the atrial systolic contraction; (2) presence of a positive pressure wave during ventricular systole which rises progressively during systole to reach a peak just prior to the reopening of the mitral valve. In some tracings, an additional early systolic pressure spike is noted. The physiologic significance of these features has been discussed.

The observation has been made that children who have sustained one episode of acute rheumatic fever may show abnormal piezocardiographic tracings and yet evince little or no clinical evidence of valvular damage.

We wish to express our appreciation to Mr. Paul Geller and Mrs. Selma Rachlin for their technical assistance.

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GENETIC STUDIES ON HYPERCHOLESTEREMIA: FREQUENCY IN A HOSPITAL POPULATION AND IN FAMILIES OF HYPERCHOLESTEREMIC INDEX PATIENTS

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HYPERCHOLESTEREMIA may be considered a common denominator for most patients with early coronary atherosclerosis.[1] Familial xanthomatosis appears to be the most severe form of this inborn error of lipid metabolism, and coronary atherosclerosis is frequent in this disorder. Uncomplicated coronary atherosclerosis in young persons probably represents a milder form of this metabolic disturbance, the elevated serum cholesterol levels, often found in these individuals, being only one important aspect of a disturbed lipid or lipoprotein metabolism.[2-6]

Until recently, studies of this subject dealt only with a single family[7] or with families of persons known to have either xanthomatosis[8] or early coronary artery disease.[9] In a preceding study[10] an attempt was made to estimate the incidence of hypercholesteremia in the population of a general hospital. Among 200 consecutive admissions to a men's ward and a women's ward of a large general hospital the incidence of idiopathic hypercholesteremia was found to be much higher than expected (17.3 per cent). An analysis of the families of the hypercholesteremic index patients revealed a high frequency of "hereditary hypercholesteremia" (5.5 per cent). It seemed necessary, therefore, not only to expand this study to a larger group of families but also to subject the data to a careful genetic and statistical evaluation, since some of the statistical criteria used in the preliminary study were open to question.

This report summarizes studies of hypercholesteremia in 250 men and 250 women, consecutive admissions to Mount Sinai Hospital, and presents an analysis of the families of fifty-nine of the seventy-five patients with idiopathic hypercholesteremia. These 500 patients include the sample of 100 men and 100 women previously reported.[10]

PROCEDURE

On admission a careful personal and family history was obtained. A physical examination was performed with particular attention to the signs and symptoms associated with idiopathic hypercholesteremia (corneal arcus, xanthelasma,

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xanthoma, and coronary artery disease). The morning after admission a specimen of venous blood was drawn after the patient had fasted for twelve hours. Total serum cholesterol was determined by the method of Schoenheimer and Sperry. Values of 280 mg. per 100 ml. or higher were considered to be hypercholesteremic.

Whenever the history, the physical examination, or the total serum cholesterol of the proband (index patient) suggested the presence of idiopathic hypercholesteremia, serum cholesterol determinations were performed on all available members of the immediate family.

RESULTS

The age of the men in the index group ranged from 12 to 79 years, average 50.9 years. The women ranged in age from 12 to 88 years, average 48.1 years. The cholesterol level of the men varied from 75 to 512 mg., average 215 mg. per 100 ml. Among the women there was a range from 85 to 983 mg., average 230 mg. per 100 ml. The basic diseases of these patients were as follows: cardiovascular-renal, ninety-one men, seventy-nine women; infectious, forty-seven men, thirty-one women; neoplastic, twenty-eight men, twenty-five women; endocrine, six men, thirty women; other diseases, seventy-eight men, eighty-five women.

Ninety-seven of the 500 probands were found to have a serum cholesterol level exceeding 280 mg. per 100 ml. This group consisted of forty-one men and fifty-six women with an age range of 16 to 80 years, average 52.8 years. The serum cholesterol of these hypercholesteremic patients varied from 280 to 983 mg., average 348 mg. per 100 ml. For purposes of more detailed analysis this group was subdivided into: (1) those with a disease commonly associated with hypercholesteremia; (2) those with idiopathic hypercholesteremia whose families could not be surveyed; and (3) those with idiopathic hypercholesteremia whose families were surveyed at least in part.

Twenty-two of these ninety-seven patients, eight men and fourteen women, were suffering from diseases commonly associated with hypercholesteremia (Group 1). Their ages ranged from 16 to 86 years, average 50.7 years; their serum cholesterol levels varied from 280 to 983 mg., average 381 mg. per 100 ml. In these twenty-two patients there were fourteen instances of intra- or extrahepatic obstruction associated with icterus, four instances of nephrosis, and four endocrine disorders (Sheehan's syndrome, Cushing's syndrome, and two with uncontrolled diabetes).

The distribution of the serum cholesterol levels of the remaining 478 patients is presented in Table I. The distributions of the values for the men and women patients are not significantly different ($X^2_{12} = 10.664$, $P \backsimeq 0.50$). If the procedure used previously[10] is followed, serum cholesterol levels of 280 mg. per 100 ml. or higher are considered to be hypercholesteremic. Thirty-two of the 242 men and forty-three of the 236 women patients had cholesterol levels of 280 mg. or greater (Table I), corresponding to percentage frequencies of 13.2 and 18.2, respectively. These frequencies are not significantly different ($X^2_1 = 2.077$, $P > 0.10$). The frequency of hypercholesteremia among the 478 patients is 15.7 per cent ($75/478 \times 100$).

TABLE I. SERUM CHOLESTEROL LEVELS OF 478 PROBANDS

SERUM CHOLESTEROL MG. PER 100 ML.	MEN		WOMEN		MEN AND WOMEN	
	NO.	(%)	NO.	(%)	NO.	(%)
60– 79	1	0.4	0	—	1	0.2
80– 99	2	0.8	2	0.8	4	0.8
100–119	6	2.5	6	2.5	12	2.5
120–139	17	7.0	13	5.5	30	6.3
140–159	28	11.6	15	6.4	43	9.0
160–179	26	10.5	28	11.9	54	11.3
180–199	41	17.0	32	13.6	73	15.3
200–219	29	12.0	32	13.6	61	12.8
220–239	26	10.5	35	14.8	61	12.8
240–259	15	6.4	16	6.8	31	6.6
260–279	19	7.9	14	5.9	33	6.9
280–299	14	5.9	18	7.6	32	6.7
300–319	7	2.9	8	3.4	15	3.1
320–339	5	2.1	5	2.1	10	2.1
340–359	2	0.8	3	1.3	5	1.0
360–379	3	1.3	2	0.8	5	1.0
380–399	0	—	3	1.3	3	0.6
400–419	1	0.4	1	0.4	2	0.4
420–439	0	—	3	1.3	3	0.6
Total	242	100.0	236	100.0	478	100.0

The frequency of idiopathic hypercholesteremia while higher than one might have expected is in agreement with the first sample of 200 probands in which hypercholesteremia was found in 17.3 per cent. As was previously stated[10] this figure is more likely to be an underestimate than an overestimate, since the probands with diseases associated with hypercholesteremia were eliminated from consideration while the few probands with conditions which might have lowered the serum cholesterol level (fever, malnutrition, loss of weight, etc.) were included.

No attempt was made to examine the families of the nonhypercholesteremic probands, inasmuch as this information was not necessary to answer the twofold question which was the object of the study, namely, (a) to establish whether or not there is an increased incidence of hypercholesteremia among the relatives of hypercholesteremic patients as compared to normal persons, and (b) if an increased incidence exists, to determine what role genetic factors play in causing it.

The first point may be established by making use of the reasonable assumption that the incidence of idiopathic hypercholesteremia is at least as great among a hospital population as among a population of well people. The data of Keys and associates[11a] which became available after ours were collected, and unpublished data we are now gathering in a survey of a healthy population tend to validate this assumption. In the sample of Keys and associates five per cent were hypercholesteremic by definition. Using their standards for our probands we found 12 per cent hypercholesteremic (Table IV). Among 169 healthy individuals studied thus far in a new survey now being conducted in Staten Island, we have found 13 per cent to be hypercholesteremic.

If the frequency of hypercholesteremia among the relatives of hypercholesteremic patients proves to be significantly greater than the frequency among the entire sample of probands, it follows that the frequency is significantly greater than that among a random sample of well people. True, we do not know how much greater, but we are not concerned with that question at this time. The second point can obviously be treated without investigating the relatives of the normocholesteremic probands.

A vigorous attempt was made to examine all available (i.e. surviving or living in or close to New York) immediate relatives of the seventy-five hypercholesteremic patients. No relatives of sixteen of these patients, eight men and eight women, could be examined.

The ages of these sixteen patients (Group 2) varied from 34 to 80 years, average 55.4 years. The total serum cholesterol ranged from 280 to 430 mg., average 321 mg. per 100 ml. In all of these patients the possibility of hereditary hypercholesteremia arose, but in no case was further examination possible. This was usually due to the fact that all the family members lived in widely separated areas throughout the country, and sometimes throughout the world. In some cases there was no living family member. Occasionally an uncooperative individual was encountered, who, without any stated reason, objected to being studied. This group emphasizes one of the greatest difficulties in a genetic study of this type, namely, the inability to obtain data on all family members.

Table II presents the data concerning the remaining fifty-nine patients (Group 3) and their relatives. In this group there were twenty-five men and thirty-four women. Their ages ranged from 33 to 80 years, average 54.8 years. Their total serum cholesterols ranged from 280 to 432 mg., average 320 mg. per 100 ml. Cholesterol determinations were made on a total of ninety-seven siblings and 110 children of these patients. Among these 110 children there was one pair of identical twins (see patient # 31 Table II); these were counted as a single zygote for purposes of analysis. The frequency of hypercholesteremia among the siblings was 51.5 per cent (50/97 x 100) and among the children 29.4 per cent (32/109 x 100). Both these frequencies are significantly higher than that found among the 478 patients; in each case P is less than 0.001. In contrast to the probands, their siblings and children were essentially healthy persons who were examined on an ambulatory basis.

After this study was almost completed, Keys and associates[11a] and Kornerup[11b] published their studies on the relationship between serum cholesterol level and age. The definition of hypercholesteremia used above did not take into account this fact. The work of Keys and his colleagues represents the first attempt to survey the blood cholesterol levels of a large population in relation to age. We have, therefore, repeated the entire analysis taking age into account and using their figures as a standard. We realize that the standards may not be entirely appropriate for our sample which is ethnically and socio-economically different, but thus far we have no evidence to indicate that they would lead to erroneous conclusions when applied to populations within the United States,[11a] or England.[13]

TABLE II. FIFTY-NINE HYPERCHOLESTEREMIC PROBANDS AND THEIR FAMILIES

PATIENT	SEX AGE COLOR NATIVITY	JEWISH OR NON-JEWISH	DIAGNOSIS	PERTINENT CLINICAL AND LABORATORY FINDINGS	SERUM CHOL.	FAMILY MEMBERS*		
						SIBLINGS	CHILDREN	OTHERS
1. JS	M 50 W Austria	J	Acute myocardial infarction; arteriosclerotic heart disease	ECG characteristic of infarction	327	S 54 286 S 52 205 B 45 345	Sn 20 212	
2. DG	M 37 W Argentina	J	Malignant hypertension and encephalopathy	BP 192/126; ECG showed myocardial damage	284	B 48 292 S 43 127 S 41 317 B 39 NE		
3. FF	M 58 W Russia	J	Primary polycythemia; duodenal ulcer; diabetes mellitus; hypertension	BP 206/100; PZI U40 daily	306	S 52 313 S 50 270	Sn 39 241 D 37 296 D 35 180 2 CNE	W 57 257
4. ES	M 48 W Germany	NJ	Bronchiectasis	Corneal arcus; xanthelasma	303	B 52 360 3 B NE 5 S NE	D 22 328 Sn 20 185	W 43 280
5. MW	M 62 W Germany	J	Acute myocardial infarction	BP 170/100; ECG diagnostic of infarction	298	B 57 336 B 52 NE	D 35 253 D 33 207 D 29 292 D 26 259	
6. LF	F 48 W U. S.	J	Kyphoscoliotic heart disease		329	S 51 323 B 47 225 S 44 281 S 38 237		
7. AD	F 74 W Russia	J	Acute myocardial infarction; arteriosclerotic and hypertensive heart disease	Corneal arcus; xanthelasma; died 24 hours after admission	340		Sn 57 321 D 54 376 Sn 52 331 Sn 46 318 Sn 44 312 D 40 293 Sn 39 349	GD 27 312 GD 23 331

*Data of examined family members include relationship to proband, age, and total serum cholesterol (mg. per 100 ml.) in that order.

Table II continued on following pages.

TABLE II. FIFTY-NINE HYPERCHOLESTEREMIC PROBANDS AND THEIR FAMILIES (CONTINUED)

PATIENT	SEX AGE COLOR NATIVITY	JEWISH OR NON-JEWISH	DIAGNOSIS	PERTINENT CLINICAL AND LABORATORY FINDINGS	SERUM CHOL.	FAMILY MEMBERS		
						SIBLINGS	CHILDREN	OTHERS
8. BL	F 80 W Russia	J	Arteriosclerotic and hypertensive heart disease; congestive heart failure	Corneal arcus; ECG showed myocardial damage	301		D 53 286 D 47 295 D 45 247 1 Ch. NE	
9. SG	F 58 W U. S.	J	Essential hypertension; obesity	BP 196/120	393	B 62 229 S 61 257 S 54 251 B 53 235 S 47 251 B 45 283 S 43 240 S 40 289 S 56 NE	Sn 39 270 Sn 33 263 Sn 29 321 2 Ch. NE	
10. AB	F 63 W Austria	J	Acute myocardial infarction; arteriosclerotic heart disease; congestive heart failure	ECG characteristic of infarction	340	B 67 419 B 58 350 B 53 317 B 46 336	Sn 39 250 D 38 226 D 32 281	
11. DN	F 43 W Russia	J	Rheumatic heart disease; cerebral embolus	Corneal arcus; BP 160/0; ECG showed myocardial damage; died of cerebral embolus	286	S 56 322 B 54 369 S 52 349 B 50 270		Np 27 313
12. JA	F 46 W U. S.	J	Paroxysmal auricular fibrillation		302	S 59 418 S 54 323 S 53 235 S 49 281 B 46 192 B 60 NE		
13. MS	M 67 W Austria	J	Arteriosclerotic heart disease	Corneal arcus; BP 148/78	331	B 69 241 S 67 350 B 63 281 B 57 NE		Np 31 302

14. HS	M 73 W Russia	J	Arteriosclerotic and hypertensive heart disease; diabetes mellitus	Corneal arcus; BP 170/90; old myocardial infarction	371	S 64 284 B 60 NE	Sn 51 323 D 43 225 D 38 240 Sn 33 249	Np 41 271
15. PM	M 35 W U. S.	NJ	Malignant hypertension	BP 250/160	361	B 33 301 B 32 310		M 70 319
16. BK	F 51 W Russia	J	Diabetes with acidosis	Hepatomegaly; BP 120/80	432	B 54 195 S 50 247 B 48 328 B 44 368 S 40 320 S 38 270	D 32 212 Sn 29 225 Sn 21 198	M 75 347
17. SI	M 41 W Hungary	NJ	Arteriosclerotic heart disease	Arcus senilis; BP 115/85	410	S 48 420	Sn 12 318	W 33 209
18. TS	M 74 W Russia	NJ	Acute myocardial infarction	BP 120/90	347		Sn 48 318 Sn 38 315 D 37 285 D 35 261 D 34 249 D 31 217	W 71 278
19. SR	F 34 W U. S.	J	Hypertensive heart disease	BP 240/140	286	S 45 273 S 42 289 S 40 236 B 39 315	D NE	M 75 266
20. AM	F 45 W U. S.	J	Hypertension; post-sympathectomy cholelithiasis	Arcus senilis; BP 210/130	310	S 50 NE S 49 332 S 44 425	Sn 23 180	
21. LL	M 42 W Sweden	J	Acute myocardial infarction; hypertensive heart disease	BP 184/142	316	B 45 232 B 44 293 S 38 260 B 36 317	1 C NE	M 69 340
22. BM	F 58 W U. S.	J	Hypertension; undiagnosed fever	Xanthelasma; BP 170/100	387	S 60 405 S 46 327	Sn 30 263	
23. IB	F 61 W Hungary	J	Acute myocardial infarction; diabetes; cholecystitis	Arcus senilis; BP 148/80	296		D 42 291 Sn 40 320 Sn 32 258	

TABLE II. FIFTY-NINE HYPERCHOLESTEREMIC PROBANDS AND THEIR FAMILIES (CONTINUED)

PATIENT	SEX AGE COLOR NATIVITY	JEWISH OR NON-JEWISH	DIAGNOSIS	PERTINENT CLINICAL AND LABORATORY FINDINGS	SERUM CHOL.	FAMILY MEMBERS		
						SIBLINGS	CHILDREN	OTHERS
24. FW	F 48 W England	J	Acute myocardial infarction; pulmonary infarction		301	S 50 408 S 48 239 S 45 334		
25. MF	F 34 W U. S.	J	Thrombophlebitis 3 weeks postpartum		289	S 36 308 B 31 299 B 30 251 S 29 243		F 60 409
26. BZ	F 66 W Russia	J	Hypertensive heart disease; diabetes; heart failure	BP 250/125	399	B 65 NE	D 40 262 Sn 39 350 D 36 288	
27. HH	F 68 W Germany	J	Arteriosclerotic heart disease; diabetes mellitus; heart failure		280	S 66 245	D 46 303 Sn 45 349 D 36 291 1 C NE	
28. JS	M 45 W U. S.	J	Diabetes mellitus	Convulsions; focal lesion on EEG	303	S 55 299 B 54 316 S 43 291 S 39 374 S 48 NE		Ne 26 244
29. JD	M 46 W U. S.	NJ	Jejunal ulcer	Corneal arcus; anemia	292	S 40 240 S 35 NE	Sn 17 205 2 C NE	W 44 184
30. SM	M 51 W U. S.	J	Acute myocardial infarction	ECG characteristic of infarction	300	S 46 NE	Sn 15 210	
31. WD	M 44 W U. S.	J	Essential hypertension	BP 200/116	316	B 54 NE S 49 NE S 47 NE	D 19 212 D 16 233* D 16 233* D 14 185 2 C NE	W 42 263

*Identical twins: counted as one individual.

32. JP	M 57 W England	NJ	Hypertensive, arteriosclerotic heart disease	BP 220/130; ECG shows damage	298	S 47 319 4 B NE 1 S NE			
33. IK	M 50 W Poland	J	Arteriosclerotic heart disease	Xanthelasma	288		Sn 22 200 D 19 320 D 25 NE	W 47 319	
34. JL	M 58 W Russia	J	Arteriosclerotic heart disease; carcinoma of bladder	Previous myocardial infarction	323	B 57 NE	D 26 228 Sn 20 281 D 16 212		
35. CS	F 60 W Russia	J	Hypertensive heart disease; gastric ulcer	BP 156/86	302	S 67 NE B 65 NE	Sn 38 212 D 36 192 D 33 233 D 31 186 Sn 28 143		
36. CB	F 56 W Austria	J	Hypertensive, arteriosclerotic heart disease	BP 150/90; ECG showed myocardial damage	433	S 65 219 B 48 274 2 S NE	D 37 198		
37. NM	F 38 W U. S.	J	Hypertension	BP 240/110; ECG showed myocardial damage	315	S 36 272 B 43 NE S 38 NE	Sn 14 187	H 41 265	
38. RS	F 72 W Hungary	J	Hypertensive heart disease	Corneal arcus; BP 210/96	371	S 65 324 1 B NE	2 C NE		
39. AS	F 66 W Italy	NJ	Hyperthyroidism; hypertensive, arteriosclerotic heart disease; diabetes	Xanthelasma; BP 185/90; PZI U10; BMR plus 58%	297	S 69 NE	Sn 42 309 D 40 243 D 38 229 2 C NE		
40. FM	M 33 W Italy	NJ	Kleinfelter's syndrome	Corneal arcus; atrophic testes; mental defect	369	S 44 224 B 35 225		M 71 279	
41. RK	F 65 W Austria	J	Hypertensive, arteriosclerotic heart disease; diabetes; heart failure; cataracts	Corneal arcus; BP 180/92	331	B 74 187 B 70 245 S 72 NE	Sn 45 160 D 39 198 D 33 192 1 C NE	Np 42 236	
42. SS	F 45 W Austria	J	Hypertensive arteriosclerotic heart disease	BP 200/110	289	2 S NE	D 23 220 Sn 18 250	H 48 310	

TABLE II. FIFTY-NINE HYPERCHOLESTEREMIC PROBANDS AND THEIR FAMILIES (CONTINUED)

PATIENT	SEX AGE COLOR NATIVITY	JEWISH OR NON-JEWISH	DIAGNOSIS	PERTINENT CLINICAL AND LABORATORY FINDINGS	SERUM CHOL.	FAMILY MEMBERS		
						SIBLINGS	CHILDREN	OTHERS
43. PF	F 62 W Russia	J	Acute myocardial infarction		342	B 61 237 B 60 284	D 42 237 D 41 203 Sn 33 261 1 C NE	
44. MG	M 63 W U. S.	J	Acute myocardial infarction; hypertension	BP 168/100	346	S 60 266 S 53 357 B 47 255 B 65 NE		
45. MF	M 57 W Russia	J	Hypertensive arteriosclerotic heart disease	BP 200/108; previous myocardial infarct	330	2 B NE 1 S NE	D 30 274 1 C NE	
46. BS	M 67 W Russia	J	Acute myocardial infarction; diabetes	Corneal arcus	285	S 63 NE B 57 NE	Sn 43 252 D 41 197 Sn 37 233 Sn 33 231	
47. AM	F 60 W Russia	J	Hypertensive, arteriosclerotic heart disease; diabetes; heart failure	Corneal arcus; xanthelasma; BP 155/110	313	S 76 NE B 74 NE B 70 NE S 66 NE	D 30 209 D 28 202	
48. EB	F 78 W England	NJ	Arteriosclerotic heart disease; syphilis; bronchitis	Corneal arcus; BP 180/90	281	S 72 NE 1 B NE 3 S NE	D 40 185 Sn 38 233	
49. HD	F 53 W U. S.	J	Rheumatic heart disease; pneumonia	Mitral insufficiency	284	S 52 220		
50. MV	F 61 W Ireland	NJ	Hypertension	BP 220/120	286		D 29 257	
51. TL	M 53 W U. S.	NJ	Hypertensive, arteriosclerotic heart disease	Corneal arcus; BP 160/100	315	S 70 NE	Sn 34 301 1 C NE	

52. JC	M 58 Mx Puerto Rico	NJ	Acute myocardial infarction; syphilis	Corneal arcus; BP 160/100	293	S 67 238 B 45 184	Sn 27 152 D 26 222	
53. MV	F 65 W Germany	NJ	Duodenal ulcer	Bleeding ulcer	289	4 B NE 3 S NE	D 42 322	
54. SR	F 36 W U. S.	J	Malignant hypertension	BP 250/150; blurred vision	288	S 41 213 S 39 232 S 28 180 B 26 179 S 24 259	3 C NE	
55. ML	F 56 W Russia	J	Hypertensive arteriosclerotic heart disease	BP 160/100	296	2 B NE 1 S NE	Sn 25 188	
56. MM	F 64 W Italy	NJ	Rheumatic heart disease	Corneal arcus; mitral stenosis and insufficiency	281	B 66 219 B 67 NE B 62 NE B 59 NE B 57 NE	D 37 169 D 34 175 D 32 225 Sn 30 247 D 27 204 Sn 24 249 Sn 20 212	
57. CE	F 48 N U. S.	NJ	Hypertensive heart disease; menopause	BP 210/135	280	4 S NE 1 B NE	D 32 265 1 C NE	
58. SS	F 55 W U. S.	J	Hypertensive, arteriosclerotic heart disease; diabetes; heart failure	Xanthelasma	324	B 49 228 B 60 NE B 49 NE	D 31 155 Sn 24 172 D 16 197	
59. DL	F 68 W Poland	J	Arteriosclerosis; cholecystitis		285	2 B NE 1 S NE	Sn 53 239 Sn 48 204 Sn 45 230 D 43 293	

W = White; Mx = Mixed; N = Negro; J = Jewish; NJ = Non-Jewish. M = Male; F = Female.
ECG = Electrocardiogram; BP = Blood pressure; BMR = Basal metabolic rate; EEG = Electroencephalogram; PZI = Protamine zinc insulin.
S = Sister; B = Brother; Sn = Son; D = Daughter; C = Child; W = Wife; H = Husband.
Np = Nephew; Ne = Niece; GD = Granddaughter; M = Mother; F = Father. NE = Not examined.

Table III shows the serum cholesterol levels of the index patients in five-year-age intervals. (One patient for whom no age was available is omitted from this table). In general the values for the men and women are fairly close, and for only two age levels (58 to 62 and 63 to 67) are the differences between the mean values significant at the 5 per cent level; in these two age groups women show higher cholesterol levels than men. We thus confirm and extend the observation of Keys and associates that, with the above exception, the serum cholesterol levels of men and women are not different.

Keys and associates[11a] published computed mean values for ages 20 through 75 years at five-year intervals. These ages correspond to the central age of each

TABLE III. SERUM CHOLESTEROL LEVELS IN MG. PER 100 ML. VS. AGE OF THE 477 PROBANDS*

Age	10 TO 17			18 TO 22			23 TO 27			28 TO 32		
	N	MCL†	SEM‡	N	MCL	SEM	N	MCL	SEM	N	MCL	SEM
Men	12	161.8	8.7	12	186.9	12.3	10	188.1	12.4	10	200.7	18.5
Women	13	188.0	12.4	20	192.8	10.0	9	200.9	9.9	8	163.9	16.5
Keys[11]		—			173.7			184.4			195.1	

Age	33 TO 37			38 TO 42			43 TO 47			48 TO 52		
	N	MCL	SEM	N	MCL	SEM	N	MCL	SEM	N	MCL	SEM
Men	14	222.7	22.4	14	231.1	21.2	11	255.6	16.4	25	215.6	10.9
Women	17	202.1	12.7	16	202.5	12.8	21	229.3	10.9	24	218.1	16.7
Keys[11]		200.4			219.4			235.5			248.3	

Age	53 TO 57			58 TO 62§			63 TO 67§			68 TO 72		
	N	MCL	SEM	N	MCL	SEM	N	MCL	SEM	N	MCL	SEM
Men	29	219.0	9.2	31	202.6	11.8	35	210.1	9.4	19	192.6	12.3
Women	24	249.5	14.0	29	251.3	15.0	22	246.4	12.2	16	212.7	17.2
Keys[11]		255.7			253.3			236.7			224.6	

Age	73 TO 77			78 TO 82		
	N	MCL	SEM	N	MCL	SEM
Men	15	199.9	18.6	5	224.8	15.0
Women	10	203.4	14.3	6	248.2	28.3
Keys[11]		211.8			—	

*One proband is not included in this table because no age was available for her.

†MCL. Mean cholesterol level in mg. per 100 ml.

‡SEM. Standard error of the mean.

§Difference between the mean values for the men and women significantly different at the 5 per cent level.

age group of Table III except the first and last and are listed in the last row of the table. As stated before there exists considerable ethnic, social, and economic differences between the group examined by Keys and associates and the hospital population of this study. The former represented a sample of healthy men taken from ". . . the population in an upper midwestern metropolitan area engaged in business, professional and scholastic pursuits," while the majority of the latter were nonprofessional workers of the lower economic strata, who, in addition, were sick. Therefore, comparisons between the data of Keys and associates and the present sample must be made with considerable reservations. Nevertheless, it is of interest to note (1) that through 45 years of age the mean cholesterol values of the men probands are higher than those published by Keys and associates and that after 50 years of age the mean values are lower. The higher values are not significantly different, but some of the lower values may be different (compare age groups 48 to 52, 53 to 57, 58 to 62, and 63 to 67); (2) the values for the women are in general closer to the values of Keys and associates than are the values for the men. Because of the comparatively small differences encountered, the heterogeneity of the two samples, and the relatively small size of our sample, further analysis does not seem warranted.

Keys and associates published, in addition, serum cholesterol values which are expected to be exceeded by only 5 per cent of the population in each age group. When these values are used to define hypercholesteremia in the present sample, one finds the figures presented in Table IV. Again it is evident that the frequencies of hypercholesteremia among the men and women patients are not significantly different. Patients of less than 18 years of age or over 77 years of age are omitted because Keys and associates did not publish figures for these age groups. The frequency of hypercholesteremia for the total usable sample is 12.0 per cent. [The data of Table III in which twelve of the means (six for the men and six for the women) are arithmetically lower than those published by Keys and associates might suggest that less rather than more than five per cent of the sample would be hypercholesteremic. However, the wide scatter and the skewed distribution of the data in each age group account for this finding.] The frequency of hypercholesteremia using the values of Keys and associates among the siblings of these "hypercholesteremic" probands is 36.2 per cent (29/78 x 100) and among the children 34.0 per cent (16/47 x 100), see Table V, *A*.

These frequencies are significantly greater than those found for the index patients. They are not, however, significantly different from the corresponding

TABLE IV. THE FREQUENCY OF HYPERCHOLESTEREMIA AMONG 441 PROBANDS BASED UPON THE UPPER 5 PER CENT LEVELS PUBLISHED BY KEYS AND ASSOCIATES[11]

	TOTAL NUMBER	HYPERCHOLESTEREMIC	
		NO.	(%)
Men	225	24	10.7
Women	216	29	13.4
Total	441	53	12.0

values obtained when levels of serum cholesterol in excess of 279 mg. per 100 ml. were considered to represent hypercholesteremia (Table V, *B*). This is in agreement with our previous finding.

TABLE V. FREQUENCY OF HYPERCHOLESTEREMIA AMONG THE SIBLINGS AND CHILDREN OF THE HYPERCHOLESTEREMIC PROBANDS. HYPERCHOLESTEREMIA DEFINED BY TWO DIFFERENT METHODS (SEE TEXT)

	STANDARD USED					
	A. KEYS AND ASSOCIATES			*B.* GREATER THAN 279 MG. PER 100 ML.		
	TOTAL	HYPERCHOLESTEREMIC		TOTAL	HYPERCHOLESTEREMIC	
		NO.	(%)		NO.	(%)
Siblings	78	29	36.2	97	50	51.5
Children	47	16	34.0	109	32	29.4

It should be stressed that insofar as the values published by Keys and associates are applicable to our data only 5 per cent of the siblings and children of the patients would be expected to have elevated cholesterol levels, rather than the 36.2 per cent and 34.0 per cent respectively observed to have such elevated levels. This is merely another way of emphasizing the significant increase in the frequency of hypercholesteremia found among the siblings and children of the probands.

Our sample of 478 index patients was composed of 266 Jews (55.6 per cent) and 212 non-Jews (44.4 per cent). It may be stated that the Jewish and non-Jewish population of the Hospital presented various degrees of heterogeneity. The majority of the Jewish patients were of East European origin (Russia and Poland) while a minority were of West European origin (Germany, Holland and Belgium). The non-Jewish population consisted of persons of Italian, Irish, English, and Slavic origin; a considerable number were Puerto Ricans and approximately one-quarter were nonwhite.

Two questions arise in relation to the ethnic origin of the patients: (1) Is hypercholesteremia equally frequent among the Jewish and non-Jewish groups of patients? (2) Is the frequency of hypercholesteremia among the siblings and children respectively of the hypercholesteremic probands of these two groups the same?

The data required to answer these two questions are presented in Tables VI and VII. They show that hypercholesteremia is more frequent among the Jewish probands ($X_1^2 = 13.108$; $.02 > P > .001$) and that the frequency of hypercholesteremia among the siblings and children of the hypercholesteremic probands is not dependent upon the patient's religion or ethnic group. The significance of this observation will be discussed later.

TABLE VI. FREQUENCY OF HYPERCHOLESTEREMIA (SERUM CHOLESTEROL GREATER THAN 279 MG. PER 100 ML.) AMONG JEWISH AND NON-JEWISH PROBANDS

PROBAND	TOTAL	HYPERCHOLESTEREMIC	
		NO.	(%)
Jewish	266	56	21.0
Non-Jewish	212	19	9.0
	478	75	15.7

TABLE VII. FREQUENCY OF HYPERCHOLESTEREMIA (CHOLESTEROL LEVEL GREATER THAN 279 MG. PER 100 ML.) AMONG THE SIBLINGS AND CHILDREN OF JEWISH AND NON-JEWISH HYPERCHOLESTEREMIC PROBANDS

	SIBLINGS			CHILDREN		
	TOTAL	HYPERCHOLESTEREMIC		TOTAL	HYPERCHOLESTEREMIC	
		NO.	(%)		NO.	(%)
Jewish	86	45	52.3	81	24	29.6
Non-Jewish	11	5	45.4	28	8	28.5
Total	97	50	51.5	109	32	29.4

DISCUSSION

The question arises as to whether the increased frequency of hypercholesteremia among the siblings and children of patients with hypercholesteremia is genetically determined. It must be stated at once that the present data do not permit a conclusive answer because the familial analyses are incomplete. The number of families in which both parents could be investigated or in which the proband's spouse could be tested is too small. Furthermore, a satisfactory estimate of the frequency of hypercholesteremia in the population at large is not available at present. Studies designed to supply the necessary data for genetic and population analyses are now in progress.

At the present time it may be stated, however, that the frequency of hypercholesteremia among the siblings and children of the index patients by either of the criteria used is too high to permit an assumption of a recessive gene as the causal factor if genetic determination is involved. The assumption of a dominant gene with complete penetrance requires that somewhat more than 50 per cent of the siblings and children be hypercholesteremic. The excess over 50 per cent expected for the siblings cannot be determined without knowing the condition of both parents, and similarly it cannot be determined for the children without knowing the status of the index patients' marital partners, or alternately without knowing the frequency of the gene in the population.

The siblings show a frequency of hypercholesteremia slightly in excess of 50 per cent when hypercholesteremia is equated to serum cholesterol levels of at

least 280 mg. per 100 ml. The children do not approach 50 per cent by this standard, nor by the one based on the data of Keys and associates (Table V). Consequently, a dominant gene showing complete penetrance seems unlikely. Another requirement for a dominant gene is that the frequency of hypercholesteremia be the same among the siblings and children of the index patients. This condition is not realized when levels of at least 280 mg. per 100 ml. are used to define hypercholesteremia but is realized within statistical limits when the more accurate procedure, employing the standards of Keys and associates which take age variations into account, is used. As a working hypothesis, then, it may be assumed that hypercholesteremia in the families of hypercholesteremic probands is determined by a dominant gene with incomplete penetrance. It must be reiterated, however, that the mode of inheritance is unknown at present and remains to be worked out.

A comparison of the present study with previous observations is of interest. The results of the study of patients with familial xanthomatosis also supported the concept that this syndrome is inherited as a dominant trait with incomplete penetrance, and that hypercholesteremia rather than xanthomatosis is the principal manifestation of the inherited factor.[9b] Similarly, the studies of Wilkinson and associates[14] presented evidence that hypercholesteremia is transmitted as an incomplete dominant trait in the clan studied by them. Stecher and Hersh[12] concluded from their genetic analysis of the data of Boas and associates[9a] on hypercholesteremia among the siblings of patients with coronary artery disease under age 50 that the hypercholesteremia was transmitted via a dominant gene with incomplete penetrance. Thus the present working hypothesis is in agreement with previous observations concerning the mode of transmission of hypercholesteremia.

The finding that hypercholesteremia is as frequent among the siblings and children, respectively, of Jewish and non-Jewish hypercholesteremic index patients may well indicate that environmental factors such as different occupations, housing, and dietary patterns are not of decisive importance in determining the presence or absence of hypercholesteremia. Such a conclusion would lend support to the concept that hypercholesteremia is primarily genetically determined and that the gene leading to a disturbance of lipid metabolism which manifests itself as hypercholesteremia is more frequent among Jews than among non-Jews. It may be recalled that other disturbances of lipid metabolism such as Niemann-Pick disease (sphingomyelin lipidosis) and Gaucher's disease (cerebroside lipidosis) occur more frequently among Jews.[1,8b]

The nature of the inborn error of lipid metabolism resulting eventually in hypercholesteremia and predisposition to early atherosclerosis is unknown. Indeed, our knowledge concerning the involved enzymatic systems as well as many other aspects of synthesis and degradation of cholesterol and other lipids under normal and especially under pathologic conditions is very limited.

SUMMARY

Hypercholesteremia appears to be a common denominator for most patients with early coronary atherosclerosis. The frequency of the occurrence of this disorder and its possible genetic relationship become, therefore, important points in any studies designed to further our knowledge of coronary artery disease, particularly that occurring in the younger age groups. This report summarizes

studies of hypercholesteremia in 250 men and 250 women, consecutive admissions to the Mount Sinai Hospital, New York, and an analysis of families of fifty-nine of the seventy-five probands who were found to have idiopathic hypercholesteremia.

Serum cholesterol determinations were performed by the method of Schoenheimer and Sperry on blood drawn from patients who had fasted 12 hours. Hypercholesteremia was considered to be present if the serum cholesterol was 280 mg. per 100 ml. or greater. The age of the 250 men in the index group averaged 50.9 years, and their serum cholesterol averaged 215 mg. per 100 ml. The 250 women averaged 48.1 years, and their cholesterol 230 mg. per 100 ml. Ninety-seven of these 500 probands (41 men and 56 women) were hypercholesteremic. This group averaged 52.8 years of age, and 348 mg. per 100 ml. of serum cholesterol. Twenty-two of these ninety-seven patients were suffering from diseases associated with hypercholesteremia and were excluded from further consideration.

Of the remaining 478 probands thirty-two of the 242 men (13.2 per cent) and forty-three of the 236 women (18.2 per cent) were hypercholesteremic. The frequency of hypercholesteremia was not significantly different between the two sexes. A thorough attempt was then made to examine the immediate relatives of the seventy-five hypercholesteremic probands. No relatives of sixteen of these patients could be examined. This was usually due to the fact that there was no living family member, or that those living were scattered throughout the world and therefore unavailable.

Ninety-seven siblings and 110 children of the remaining fifty-nine hypercholesteremic probands were examined. The frequency of hypercholesteremia among the siblings was 51.5 per cent and among the children 29.4 per cent. Both these frequencies are significantly higher than those found among the 478 patients.

Since the definition of hypercholesteremia used in the preceding calculations did not take into account the fact that serum cholesterol varies with age, the analyses were repeated using data of Keys and associates[11a] in which age is taken into consideration; in these two age groups women have significantly higher cholesterol levels than men. Again it was found that the values for men and women are fairly close, differing at the 5 per cent level for only two age groups, 58 to 62 and 63 to 67. Keys and associates published serum cholesterol values which are expected to be exceeded by only 5 per cent of the population in each age group. The frequency of hypercholesteremia for the total usable sample, according to this method of analysis, was 12.0 per cent; the frequency among the siblings of the hypercholesteremic probands was 36.2 per cent and among the children 34.0 per cent. These frequencies, again, are significantly greater than those found for the index patients; but are not significantly different from the corresponding values obtained when levels of cholesterol above 279 mg. per 100 ml. were considered to represent hypercholesteremia.

Of the 478 probands 266 were Jewish and 212 were non-Jewish. Hypercholesteremia was significantly more frequent among the Jewish probands (21 per cent versus 9 per cent), but the frequency among siblings and children was not different when Jewish hypercholesteremic probands and families were compared with non-Jewish.

The mode of inheritance of idiopathic hypercholesteremia remains to be worked out. The finding that hypercholesteremia is as frequent among the sib-

lings and children of the non-Jewish hypercholesteremic probands as compared with the Jewish may indicate that environmental factors are not of too great importance in determining the presence of hypercholesteremia.

The validity of these tentative conclusions awaits the completion of a study now being done in a more representative and complete population group. However, even these preliminary observations shed some light on the complicated error of metabolism involved in hypercholesteremia and predisposition to early atherosclerosis.

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STUDIES IN CARDIOVASCULAR SYPHILIS

III. The Natural History of Syphilitic Aortic Insufficiency*

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EXTRAORDINARY as the statement may sound, the enormous world literature on the prognosis and the effect of treatment of cardiovascular syphilis is, with a few exceptions, of little value. There are two major reasons for this. The first is that most authors have tended to discuss cardiovascular syphilis as an entity, grouping together uncomplicated aortitis, all stages of aortic insufficiency and saccular aneurysm, in spite of the fact that the clinical signs, the symptomatology, and the prognosis are vastly different. Little attention has been given to factors which modify the outcome of the disease, such as, (1) those inherent in cardiovascular syphilis itself, i.e., congestive heart failure, coronary insufficiency, auricular fibrillation, and subacute bacterial endocarditis; (2) those due to associated nonsyphilitic diseases such as arteriosclerosis or essential hypertension. A few investigators have attempted to avoid these pitfalls by limiting their discussions to aortic insufficiency and/or saccular aneurysm and have attempted to deal with the complications. In this group should be included the studies of Grant,[1] the group at the Johns Hopkins Hospital,[2-4] the group at the New York Hospital,[5-7] Barnett,[8] Barnett and Small,[9] and Stratton.[10]

The second reason for the lack of value of the greater part of the literature on cardiovascular syphilis is the almost total absence of controls in attempting to evaluate prognosis or treatment in a chronic disease of the nature of cardiovascular syphilis. To estimate the efficacy of therapeutic procedures in any disease one should know accurately the prognosis in the absence of treatment. In the case of cardiovascular syphilis, this logical requirement has not been met, and information is not available.

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In 1948, a subcommittee on the treatment of cardiovascular syphilis was authorized by the Syphilis and Cardiovascular Study Sections of the National Institute of Health. The discussions of this committee were aimed at a determination of the value of penicillin in the treatment of cardiovascular syphilis. It was agreed that this could be accomplished only if there were, or could be made available to serve as controls, a group of patients with cardiovascular syphilis who had received no treatment but who were otherwise identical with the treated group. In addition, it was felt that a similar group who had received metal chemotherapy should be studied. The idea of a prospective study in which penicillin was administered to alternate patients was rejected as impractical. The only alternative, therefore, seemed to be to plan a prospective study employing penicillin in the treatment of every patient and developing a control group from retrospective study of material available in the records of several participating clinics.

Accordingly, in order to test the feasibility of such a plan, a pilot study was set up in which fifty case histories of patients with syphilitic aortic insufficiency were selected from each of eight participating clinics. A biostatistical analysis of the material so obtained immediately indicated that there was such a degree of disparity in the material from different clinics that no valid conclusions could be drawn.

It was felt, however, that the material from the New York Hospital and that from the Johns Hopkins Hospital were sufficiently similar, both in population groups and the essential organization of the Syphilis Clinics as integral parts of the Department of Medicine, to warrant further study as a source of retrospective controls.

Accordingly, the present study was set up between these two institutions, with the biostatistical collaboration and guidance of one of us (P.M.D.). In the two previous reports,[11,12] attention was directed to the methodological problems involved in the evaluation of therapy, and it was concluded that, if not impossible, it is extremely unlikely that past records may be used to provide a control group for the evaluation of therapy. There is, however, a wealth of information in these past records. It is the purpose of the present paper to inquire into the natural history of cardiovascular syphilis as revealed by these data, and it is hoped that the methods used in evaluating this material might prove of value in the study of other chronic diseases.

MATERIAL

The charts of 309 patients from the New York Hospital and of 711 from the Johns Hopkins Hospital were collected. These patients represented in each hospital the entire clinic population having aortic insufficiency thought to be due to syphilis, from 1930 to 1950 at the New York Hospital and from 1925 to 1950 at the Johns Hopkins Hospital. These patients had been carefully studied medically and were given complete physical examinations and chest roentgenograms at yearly intervals for as long as possible after initial diagnosis. At the time of this study, great pains were taken to see and examine as many of the patients as could

be located. Of those patients who had died or moved, accurate information concerning cause of death or present condition was obtained when possible from death certificate, hospital or doctor's records. A number of patients could not be located, and they were considered to be lost to the study as of the time at which they last had been seen.

The cases were reviewed by two physicians at each hospital to determine their suitability for this study. They were included in every instance when the consensus of the examining physicians was that they had had syphilitic aortic insufficiency. If they were considered also to have had saccular aneurysm or paresis, they were excluded because it was felt that these states might carry an individual prognosis which might distort the picture for aortic insufficiency alone. Patients originally considered to have had syphilitic aortic insufficiency who were later found to have had some other cause for the aortic valvular lesion were retained in the study. It was considered important to examine the disease so that it could be diagnosed clinically rather than at the autopsy table. The charts were abstracted, using the same form in both hospitals, with suitable precautions to prevent a different interpretation in the recording of the data in the two clinics. The data were gathered, tabulated on punch cards, and subjected to the analysis which is the subject of this report.

METHOD

In previous reports[11,12] it was demonstrated that the material in the two hospitals was not comparable in such fundamental variables as age groupings, sex or race, or in terms of treatment received. There was also disparity in the treatment groups in relation to the onset of symptoms and many other factors. The possibility of overcoming these disparities between the treated group and the untreated group by means of a matching process was discussed and was shown to present certain logical difficulties. In principle, at least, the same difficulties arise in attempting to evaluate the influence of prognosis of factors other than therapy. However, there is a fundamental difference between such a variable as treatment and a factor such as race which makes the employment of a matching procedure more likely to yield valid comparisons. In the case of treatment as a variable, the physician has a choice as to whether or not the patient should receive treatment. His choice was influenced by many factors related to the clinical status of the individual. For instance, before the days of penicillin therapy, arsenic was not used on certain patients who were considered too ill to withstand risks of treatment. Again, the patient's own attitude was of great importance. The principal reason for inadequate treatment was lack of cooperation. There is no assurance that they will be comparable with respect to factors such as these or other intangible elements which influence the decision to give or withhold treatment even though the treatment group and the control group may be made comparable with respect to such characteristics as age, sex, and race. On the other hand, if one wished to determine the influence of race on prognosis and made the white and nonwhite groups comparable with respect to the proportion of individuals receiving treatment, it is not improbable that they will be comparable with respect to factors which may have influenced the physician's decision to treat

the patient. Of course, there are characteristics of the patient other than race which are not influenced by the physician such as age or sex which still may not be comparable in the two groups even after matching on treatment. Some of these in turn may be matched, and one is a little more willing to take a chance on the rest because they are not related to clinical status. This is the approach of the present paper.

For the purposes of this report the groups to be compared with respect to their influence on prognosis have been matched on a proportional basis with respect to the following six variables. They are: (1) treatment for cardiovascular syphilis; (2) age at diagnosis; (3) sex; (4) race; (5) work status at time of diagnosis; and (6) presence or absence of symptoms prior to diagnosis. The matching process was carried out in such a way as to make the proportional distribution in the groups to be compared the same with respect to these six variables within the limits of chance variation. A proportional matching process was used rather than a "one to one" matching in order to conserve the size of the groups being compared.

The steps in the matching process will be illustrated by data on the influence of congestive failure on prognosis. To simplify the discussion we shall consider all of the patients divided into two groups: those with congestive failure at diagnosis and those without congestive failure at that time. The first step is to arrange the data as shown in Table I and to calculate the per cent shown in the right hand side of the table after eliminating the cases for which information was not reported with respect to congestive failure.

Examination of Table I resulted in the decision to make the "heavy metal" and "no treatment" groups have the same proportions with respect to congestive failure as the "penicillin" group, since this procedure would conserve the numbers in the latter group. In this way, Table II was prepared in which the per cent of patients with congestive failure is the same (46.21 per cent) in each of the three treatment groups.

Table II, in comparison with Table I, shows that one case would need to be withdrawn from the patients without failure who were treated with heavy metal, and 99 from the group with no treatment in failure. The withdrawing of these cases was done by using a table of random numbers. The remaining cases in the treatment groups were then combined to yield 423 individuals in the "failure" group and 492 in the "no-failure" group, these two groups now being comparable with respect to type of treatment for cardiovascular syphilis. In its essentials the process of matching the two groups on the other five variables (age, sex, race, work status, and presence of symptoms prior to diagnosis) is the same as that just described (see Appendix). As a result of this process the final number was 422 in the "failure" group and 156 in the "no-failure" group, the two groups now being comparable with respect to all six variables (the five just listed plus type of treatment for cardiovascular syphilis). These two groups were then analyzed by the usual life table procedures (Berkson) to determine mortality after diagnosis.

TABLE I. NUMBER AND PER CENT OF CASES IN EACH TREATMENT GROUP ACCORDING TO PRESENCE OR ABSENCE OF CONGESTIVE FAILURE AT DIAGNOSIS

STATUS AT DIAGNOSIS	NUMBER OF CASES IN EACH TREATMENT GROUP				PER CENT OF CASES IN EACH TREATMENT GROUP			
	PENICILLIN	HEAVY METALS	NO TREATMENT	TOTAL	PENICILLIN	HEAVY METALS	NO TREATMENT	TOTAL
With congestive failure	55	207	260	522	46.21	46.10	58.16	51.43
Without congestive failure	64	242	187	493	53.79	53.90	41.84	48.57
No record	0	4	1	5	—	—	—	—
Total	119	453	448	1,020	100.00	100.00	100.00	100.00

TABLE II. ADJUSTED NUMBER AND PER CENT OF CASES AFTER MATCHING OF THE TREATMENT GROUPS

STATUS AT DIAGNOSIS	NUMBER OF CASES IN EACH TREATMENT GROUP				PER CENT OF CASES IN EACH TREATMENT GROUP			
	PENICILLIN	HEAVY METALS	NO TREATMENT	TOTAL	PENICILLIN	HEAVY METALS	NO TREATMENT	TOTAL
With congestive failure	55	207	161	423	46.21	46.21	46.26*	46.23
Without congestive failure	64	241	187	492	53.79	53.79	53.74*	53.77
Total	119	448	348	915	100.00	100.00	100.00	100.00

*These per cents differ slightly from the others because of the rounding off process.

RESULTS

The following data may be divided into three sections. After an initial series of tables defining the material, there is an intensive investigation of the prognosis in these patients, particularly as affected by various factors surrounding the patient's status and by certain events in the course of the disease. Lastly, there is an analysis of the course in those patients who died and presentation of the autopsy data.

Period of Observation.—Ideally, in any study of survivorship it is desirable that at the time of investigation the status of all individuals in the study be known. If it is not possible to trace any sizable proportion of individuals at that time, it may be questioned whether or not those who remain under observation are representative of the entire group. Table III shows the extent to which it has been possible to follow patients in this study.

TABLE III. FOLLOW-UP OF CARDIOVASCULAR SYPHILIS PATIENTS, JOHNS HOPKINS HOSPITAL AND NEW YORK HOSPITAL

GROUPS, YEARS*	JOHNS HOPKINS			NEW YORK		
	TOTAL	NUMBER	PER CENT TRACED	TOTAL	NUMBER	PER CENT TRACED
2.5	711	607	85.4	309	217	70.2
7.5	603	510	84.6	229	148	64.6
12.5	452	379	83.8	133	81	60.9
17.5	254	215	84.6	25	19	76.0
22.5	98	83	84.7			

*The date of investigation is January 1, 1950. The 2.5 year group consists of all patients diagnosed between 1945 and 1950 (the median length of follow-up of this group being 2.5 years) plus all patients diagnosed prior to 1945; the 7.5 year group consists of all patients diagnosed between 1940 and 1945 (the median length of follow-up of this group being 7.5 years) plus all patients diagnosed prior to 1940, and so on. It was not possible to get the length of follow-up more exact than this because, unfortunately, the date of diagnosis was coded in five-year groups. The effect of this, however, is to make the percent traced lower than the true figure. The term "traced" means status known for the indicated number of years.

As indicated in the footnote to Table III, the per cents traced are lower than the probable actual figures. The table shows that about 85 per cent of Johns Hopkins Hospital patients were traced to the date of investigation, but the figure for New York Hospital patients is nearer 70 per cent. If both hospitals are combined, about 75 per cent of all patients were traced to the date of the investigation. We do not know what element of selection this may introduce into the data. Although one cannot be certain, it seems likely, however, that any selection that might be present would operate to change the level of survivorship curves rather than their relative position with respect to each other. From this standpoint it is felt that the findings of this study have value.

Risk of Hospitalization.—Another aspect of the prognosis, to some extent extraneous to the rest of the study, but of considerable practical importance, is the probability of a patient being hospitalized following the diagnosis of aortic insufficiency. In Fig. 1, again based upon the unmatched material from each clinic, this factor is explored.

At the time of diagnosis, 27 per cent and 35 per cent, respectively, of all patients at New York and Johns Hopkins Hospital were hospitalized. These high initial figures were expected for several reasons. Many patients were seen first in the wards of the hospital when they developed heart failure and were found then to have aortic insufficiency. Others were admitted for other diseases, and aortic insufficiency was an incidental finding. In each hospital, some patients were admitted routinely for treatment at or shortly after the time of diagnosis. The coding system employed in this study was such that all patients admitted during the first six months after the diagnosis of cardiovascular syphilis were coded as

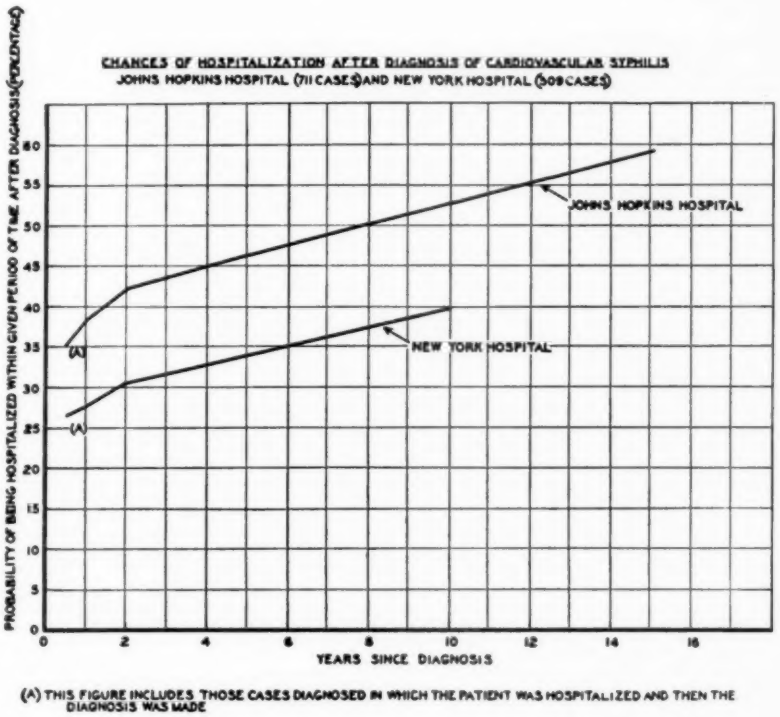

Fig. 1.—Chances of hospitalization after diagnosis of cardiovascular syphilis.

being hospitalized "at the time of diagnosis." Once the initial heavy risk of hospitalization passed, there was a steady small percentage of the patients entering the hospital. This is indicated by the slopes of the curves in Fig. 1 which are constant and the same for both hospitals. After ten years, the total percentage admitted had risen to only 40 per cent and 53 per cent, respectively, for the two clinics. The fact that the two curves so nearly parallel each other suggests that whatever the factors influencing hospitalization, they operate the same way in the two clinics. On the other hand, the difference in level of the curves may reflect the difference in method of discovery in the two clinics. The Johns Hopkins Hospital clinic had a much higher proportion of cases found because they reported for cardiovascular syphilis. (See Table VIII of Ref. 12.)

Survival After Diagnosis.—Of major interest was the over-all prognosis in aortic insufficiency. In Fig. 2 the survivorship of the entire population in each clinic is presented. It indicates what per cent of patients survived any given time period. In the preparation of this figure, the entire series of 1,020 patients is included, and no matching process was used.

Ten years after the diagnosis of aortic insufficiency, 43 per cent and 33 per cent of the patients at the New York Hospital and the Johns Hopkins Hospital, respectively, were alive. After 15 years 30 per cent and 20 per cent of the patients at the two institutions still survived. These data demonstrate that many patients with aortic insufficiency live for a much greater period of time than was commonly thought to be the case.

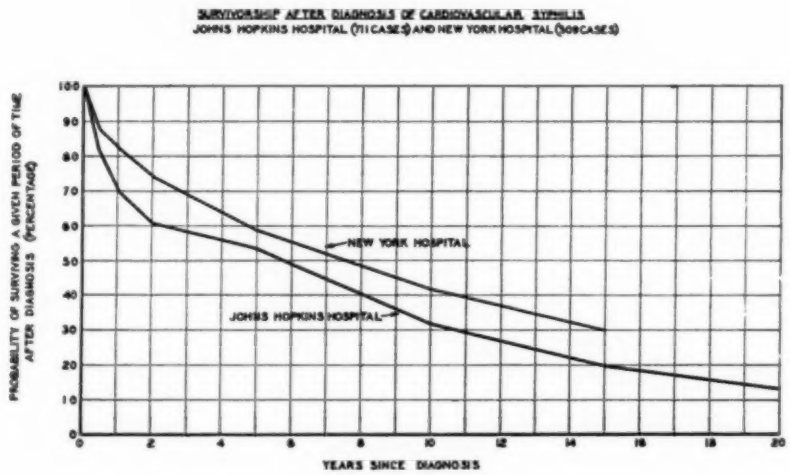

Fig. 2.—Survivorship after diagnosis of cardiovascular syphilis.

It was next desirable to examine certain factors which might affect prognosis in order to determine, if possible, why some patients survived when others did not, and whether it might be possible to predict which patients do well and which do not. Accordingly, a series of figures were drawn up using the matching process outlined in the section on method. In these figures, the effect of specific variables other than that being examined was neutralized by the matching process, so that a specific factor might be examined without influence of the matched variables on the results. These data are now presented.

Effect of Race and Sex on Survival.—Clinical opinion is uniform that Negro men with syphilitic aortic insufficiency suffer from a poorer prognosis than do other population groups. In Fig. 3 the survivorship of nonwhite men and women (with negligible exceptions all Negro) is compared with that of white men. The small total number of white men made it impossible to examine this group separately, and they were omitted from the comparison.

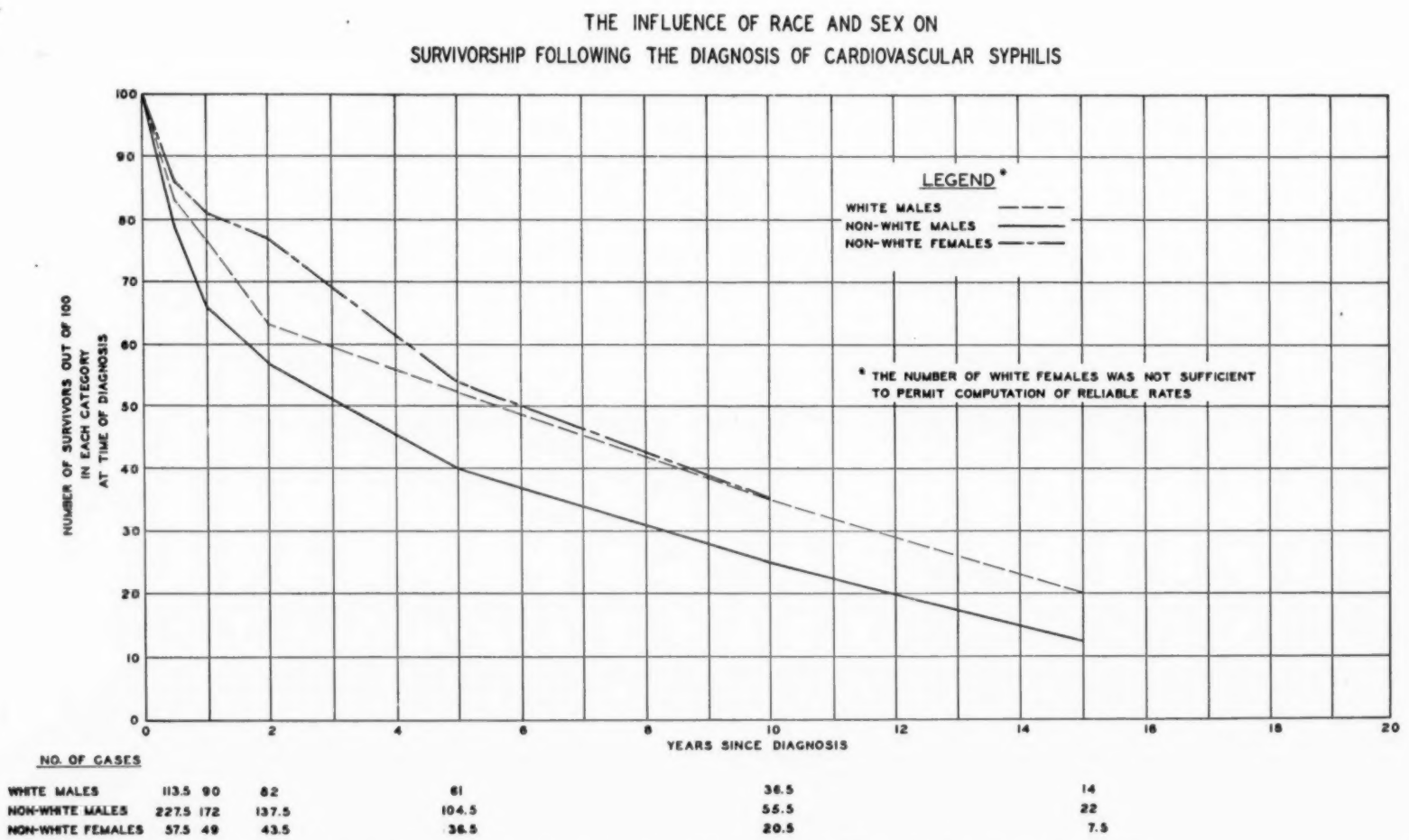

Fig. 3.—The influence of race and sex on survivorship following the diagnosis of cardiovascular syphilis.

For the first five years after diagnosis, Negro women had a better prognosis than either Negro men or white men but the latter had a better prognosis than Negroes. After this time white men and Negro women had an essentially similar survival rate and continued to do better than Negro men. The difference between Negro men and white men, however, was less than the clinicians involved in this study anticipated. In this respect, it is to be remembered that differences associated with treatment status and the other variables mentioned previously have been eliminated.

Effect of Age on Survival.—It is frequently said that patients who develop syphilitic aortic insufficiency at an early age have a poorer prognosis than those who are older when first seen. In Fig. 4 an analysis of this problem was carried out for matched cases from both hospitals.

There was a sharp drop in the survival of the younger patients during the first year, but thereafter they enjoyed a slightly better prognosis than the older patients. Of those patients first discovered to have aortic insufficiency when less than 40 years old, about 54 per cent survived 5 years, 35 per cent survived 10 years, and 30 per cent survived 15 years. Among those patients first seen when over 60, the 5, 10 and 15 year survival rates were only 42 per cent, 21 per cent and 12 per cent, respectively.

When examining the influence of age on the prognosis, one must consider the normal increase in mortality as age advances. Therefore, when dealing with a long follow-up in patients whose age varies widely, it is more meaningful to compare the chance of survival of a patient to that of a standard population than simply to compute death rates. The standard population chosen for comparison was that of the life table for the population of the United States, 1939-1941.

In Fig. 5 the chances of survival for a given time period in the patients under study for each age group were compared with those of a standard population. The curves are computed on the basis of the ratio of the probability of survival among the cardiovascular syphilis patients of this study to that of the life table population of comparable age groups.

These data show that at whatever age aortic insufficiency was discovered, the chance of survival was much less than for the standard population. The initial high death rate among the younger patients already seen in Fig. 4 was reflected in the poor comparative survival in these patients during the first two years after diagnosis. During this period the younger and older patients had roughly similar chances. After the first two years, the younger patients were again a little better off than those over 50 years of age at the time of diagnosis. For those under 50 years of age when found to have aortic insufficiency, the chance of ten-year survival was only about two-fifths of the rate of the standard population. In those patients found to have aortic insufficiency when 60 or more years of age, the chance of a ten-year survival was only about one-fifth that of individuals of the same age in the standard population.

Effect of Work Status on Survival.—It has often been stated that patients doing light work have a better prognosis than laborers. In Fig. 6 the prognosis of patients doing heavy work and light work is compared. In the original coding

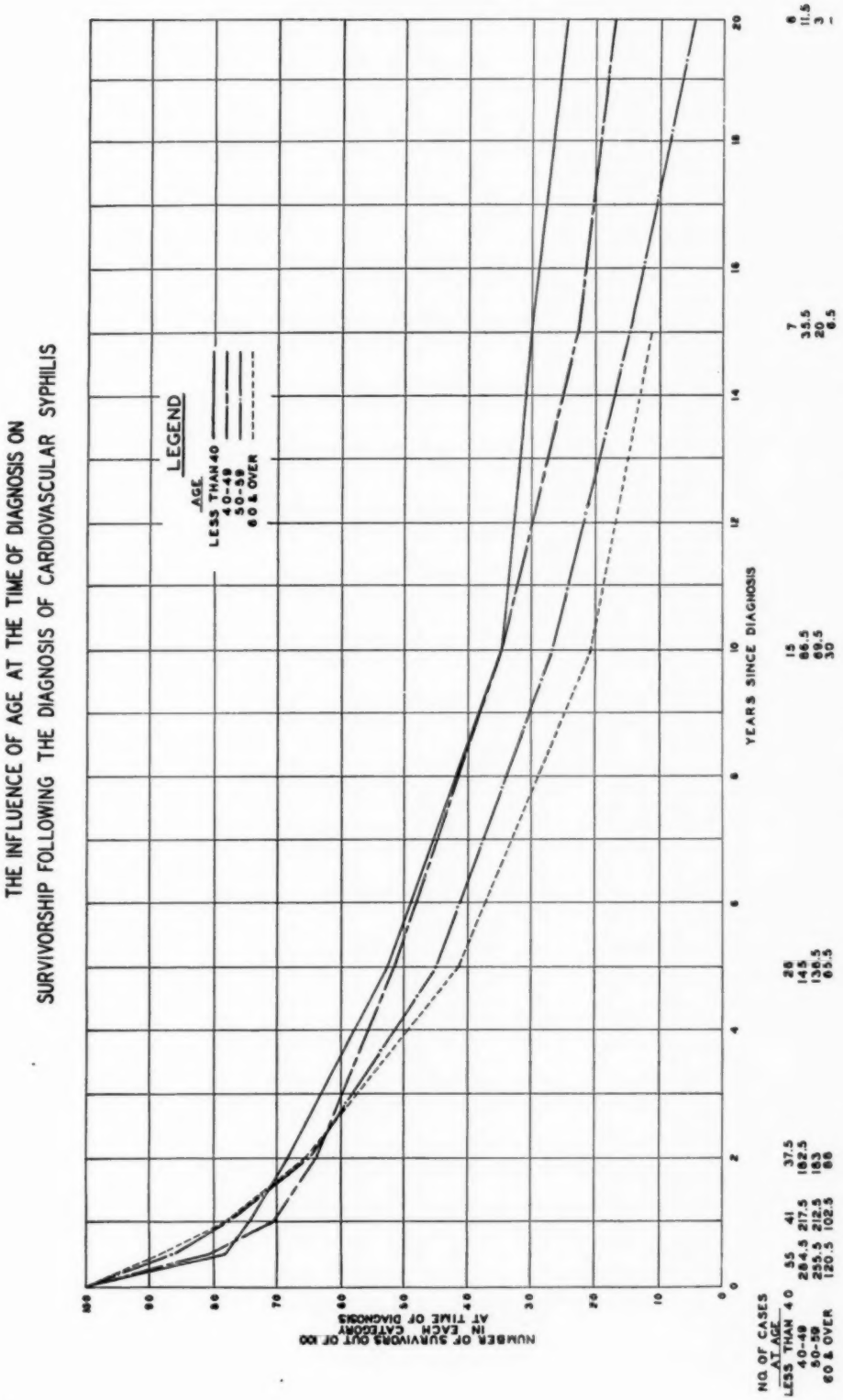
THE INFLUENCE OF AGE AT THE TIME OF DIAGNOSIS ON
SURVIVORSHIP FOLLOWING THE DIAGNOSIS OF CARDIOVASCULAR SYPHILIS
LEGEND
AGE
LESS THAN 40
40-49
50-59
60 & OVER
NUMBER OF SURVIVORS OUT OF 100 IN EACH CATEGORY AT TIME OF DIAGNOSIS
YEARS SINCE DIAGNOSIS
NO. OF CASES AT AGE
LESS THAN 40 55 41 37.5 20 15 7 0
40-49 284.5 217.5 182.5 145 86.5 35.5 11.5
50-59 255.5 212.5 153 136.5 69.5 20 3
60 & OVER 120.5 102.5 86 65.5 30 6.5 1

Fig. 4.—The influence of age at the time of diagnosis on survivorship following the diagnosis of cardiovascular syphilis.

from the clinical charts the work status was estimated as accurately as possible from the data recorded at the time of diagnosis, onset of symptoms, and before and after treatment. This, of course, was subject to some error, and the results are relative. In general, those patients who had previously been laborers continued to be such until disease itself made it impossible for them to work. For the purposes of Fig. 6, it was felt that those patients doing heavy work at two points, usually occurring early in the course of their observed disease, could be compared with those doing light work at those same times. The points of reference selected were the onset of symptoms and the time of the beginning of treatment. It should be noted that a majority of the patients developed symptoms prior to diagnosis and that treatment in almost every case was started shortly after the diagnosis had been made. A third group doing heavy work at the onset of symptoms and light work at the start of treatment was introduced for comparison.

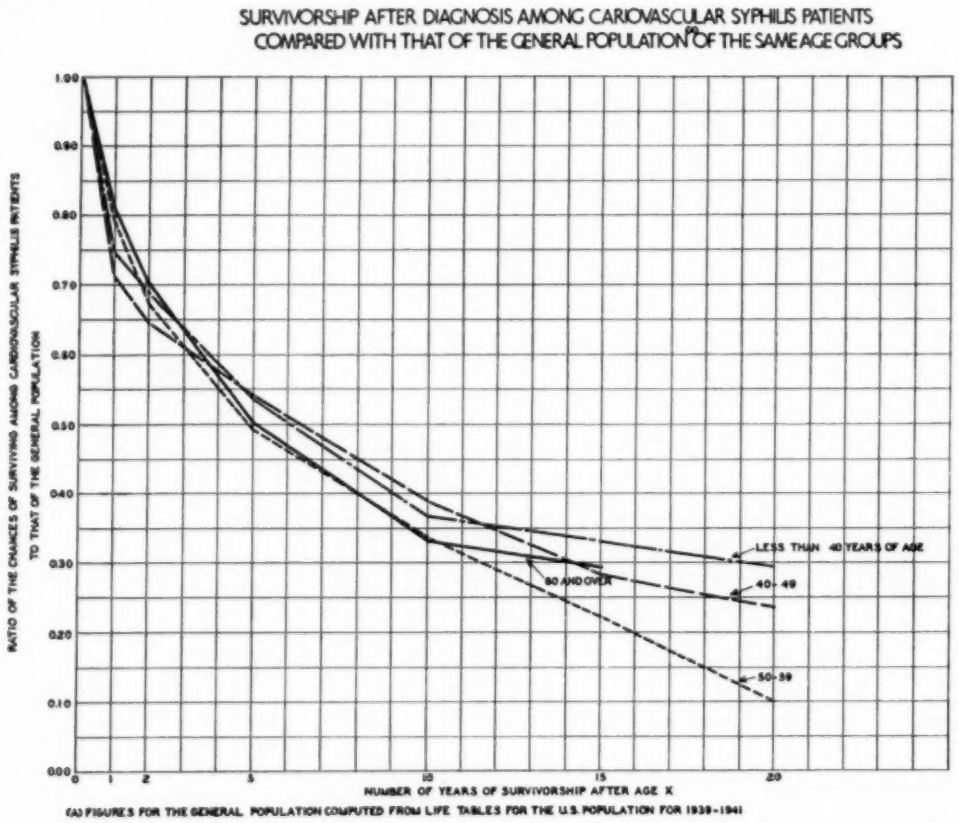

Fig. 5.—Survivorship after diagnosis among cardiovascular syphilis patients compared with that of the general population of the same age groups.

This method of selecting patients drastically reduced the number of cases available for analysis. It was considered necessary, therefore, to group together the work categories. In the original coding the patients had been classified as doing heavy, moderate, light, sedentary, and no work. In Fig. 6, the original

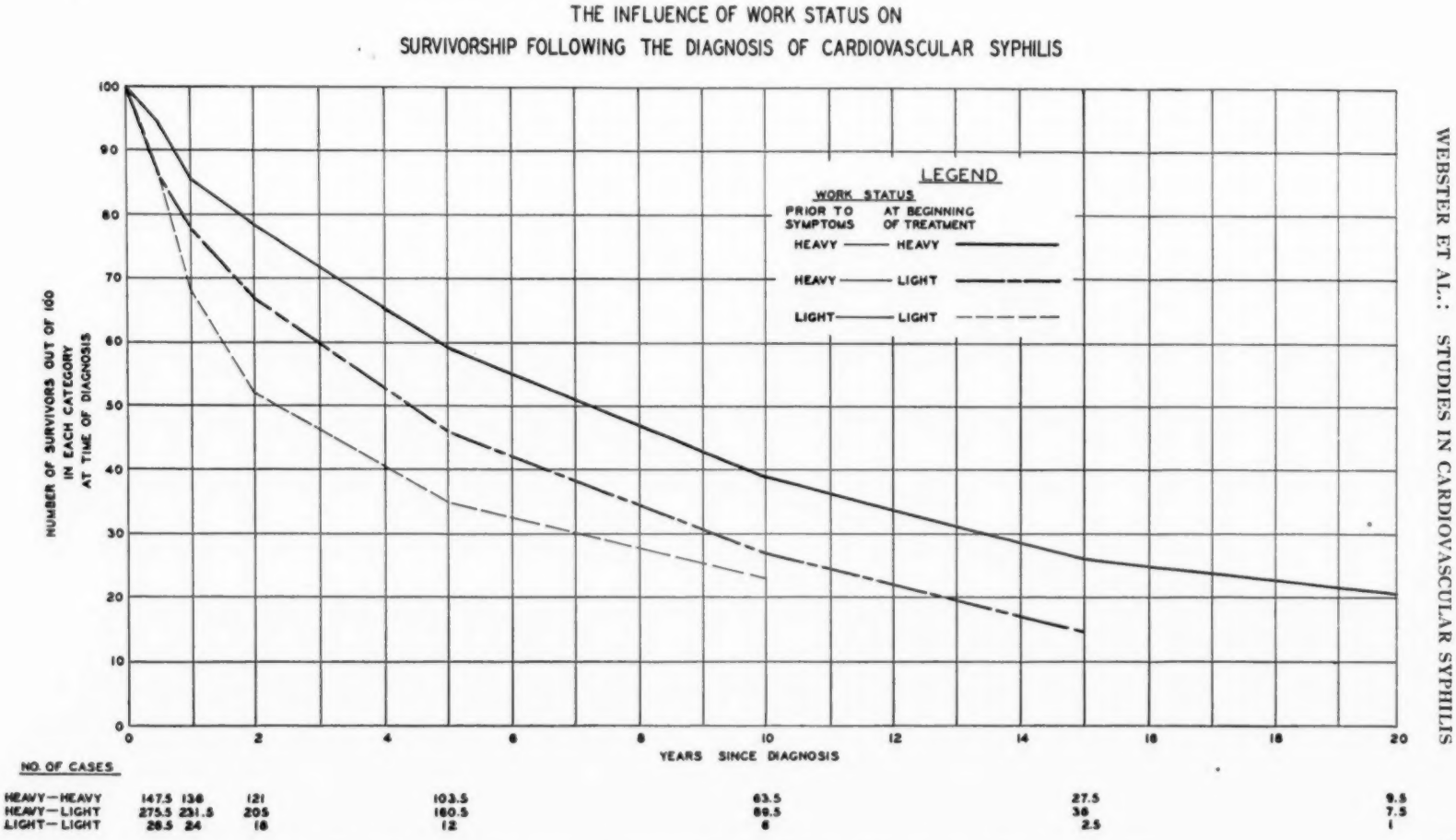
THE INFLUENCE OF WORK STATUS ON
SURVIVORSHIP FOLLOWING THE DIAGNOSIS OF CARDIOVASCULAR SYPHILIS
LEGEND
WORK STATUS
PRIOR TO SYMPTOMS
AT BEGINNING OF TREATMENT
HEAVY — HEAVY
HEAVY — LIGHT
LIGHT — LIGHT
NUMBER OF SURVIVORS OUT OF 100 IN EACH CATEGORY AT TIME OF DIAGNOSIS
YEARS SINCE DIAGNOSIS
NO. OF CASES
HEAVY—HEAVY 147.5 136 121 103.5 63.5 27.5 9.5
HEAVY—LIGHT 275.5 231.5 205 160.5 86.5 36 7.5
LIGHT—LIGHT 28.5 24 18 12 6 2.5 1

Fig. 6.—The influence of work status on survivorship following the diagnosis of cardiovascular syphilis.

heavy and moderate groups are combined and charted as "heavy" and the light, sedentary and no work groups are recorded as "light." To our initial surprise, it was found that 38 per cent of those people doing heavy work during the early phase of their disease survived ten years, whereas only 23 per cent of those doing light work survived this time.

An explanation of this paradoxical finding was sought by further analysis of the material. The possibility of a hidden classification was explored by comparing the number of patients having dyspnea on slight exertion in the different work categories of the original coding. As explained above, the group of patients doing light work in Fig. 6 consisted of many originally coded as doing light and sedentary work, but a larger group of patients doing no work at all. The patients in this latter group were separated in the analysis with respect to cardiac status in an effort to see if they were weighting the over-all material. These data are presented in Table IV.

TABLE IV. PREVALENCE OF SEVERELY ILL CARDIAC PATIENTS* IN EACH WORK STATUS GROUP AT BEGINNING OF TREATMENT, JOHNS HOPKINS HOSPITAL AND NEW YORK HOSPITAL

WORK STATUS OF BEGINNING OF TREATMENT FOR C.V.S.	JOHNS HOPKINS		NEW YORK		TOTAL	
	TOTAL CASES	FUNCTIONAL STATUS CLASSED AS GRADE 3 OR 4 (%)	TOTAL CASES	FUNCTIONAL STATUS CLASSED AS GRADE 3 OR 4 (%)	TOTAL CASES	FUNCTIONAL STATUS CLASSED AS GRADE 3 OR 4 (%)
Heavy	196	15.8	58	6.9	254	13.8
Light	53	20.8	65	15.9	118	17.8
None	448	53.6	47	25.5	495	50.9

*Severe cases are considered to be those in which functional status at the beginning of treatment was classed as Grade 3 or 4 according to the American Heart Association classification. Cases in which either work status or functional status was unknown are omitted from the table.

The "light" work group contained only about one-fourth as many patients as did the group doing no work, and though the heavy work and light work groups had somewhat similar numbers of severely symptomatic cardiacs (13.8 per cent and 17.8 per cent), the group doing no work had a very high proportion (50.9 per cent) of severely ill cardiac patients. This is the largest group and had been added to the light group to compute the patients charted as doing "light work" in Fig. 6. It is obvious that this distorts the result. The apparent poor prognosis of patients doing light work is due to the larger number of patients who could do no work because they were disabled by cardiac symptoms.

The great majority of the patients were laborers and for economic reasons were unable to avoid heavy physical exertion until forced to do so by the symptoms of their disease. When they present themselves for treatment they are classified as doing no work. In other words, there is a self-selection with respect to work status by the time the patients present themselves at the clinic, and it is this that results in the reversal of the expected relationship between work status

and chances of survival. It is quite possible that if information could be obtained on work status at time of onset of the disease, the expected relationship would hold.

It should be emphasized that since work status is one of the variables that have been matched in assessing the influence of other factors on prognosis, its effect has been neutralized or "taken out," in as much as the patients in each work group have been proportionately distributed among the other groups being compared. It is also of interest that the hidden classification here demonstrated bears out the discussion in the previous paper concerning the difficulties of matching with respect to variables which may be controlled by either the patient or the physician.

Effect of the Complications of Cardiovascular Syphilis on Survival.—The prognosis of patients with aortic insufficiency has been considered so far in a general way and related to such factors as age, sex, race, and work status. A consideration of the effect of certain complications which developed during the course of the disease will be presented. The two complications which were found to be significant in this study were congestive heart failure and angina pectoris. An attempt to evaluate the effect of auricular fibrillation was unsuccessful as there were inadequate numbers of patients for analysis. The same difficulty arose when an attempt was made to examine the prognosis of those patients with abnormal electrocardiograms.

Of the 1,020 patients studied, 762 developed symptoms related to cardiac disease at some time during the time they were followed. Of course, many developed more than one symptom. There were 522 who were considered to have had evidence of cardiac failure. No uniform criteria for failure could be used as the description in the charts was occasionally incomplete. In general, patients were considered to have been in failure when they had had dependent edema, dyspnea on climbing one or two flights of stairs, or orthopnea. Angina pectoris was described in 213 patients. In seventy-two patients the presence of auricular fibrillation was recorded.

Several practical questions could be answered about each of these factors mentioned. The course of those patients not developing a complication such as failure at any time could be compared with that of the group as a whole. This would not be of much practical use in predicting the course of a patient first seen without failure, as it would not be possible to know at that time what would happen to him in the future. Therefore, the material was divided into four groups. The first included those patients who never developed failure at any time while under observation; second was the group free of failure at the time of diagnosis regardless of whether or not they later developed failure; third were those in failure at the time of diagnosis; and fourth were all those having congestive failure at the time of diagnosis plus those who developed failure sometime after diagnosis. This classification not only allows one to predict the average expectancy for a patient who is seen first free of failure but allows his prognosis to be re-evaluated at such time as failure develops. The same breakdown was carried out for the other complications examined.

Effect of the Development of Symptoms on Survival.—It seemed desirable to have some over-all category to separate the clinically well from the sick patients. To do this they were divided into symptomatic and asymptomatic groups. The symptomatic group included all patients who had the symptoms usually associated with cardiac disease (chest pain, dyspnea, orthopnea, ankle edema) and therefore included the patients in the "angina" and "failure" group as well as a number of patients with other cardiac symptoms. It should be noted that such a group included those patients who had associated symptomatic hypertensive and arteriosclerotic heart disease as well as those with symptoms from aortic insufficiency.

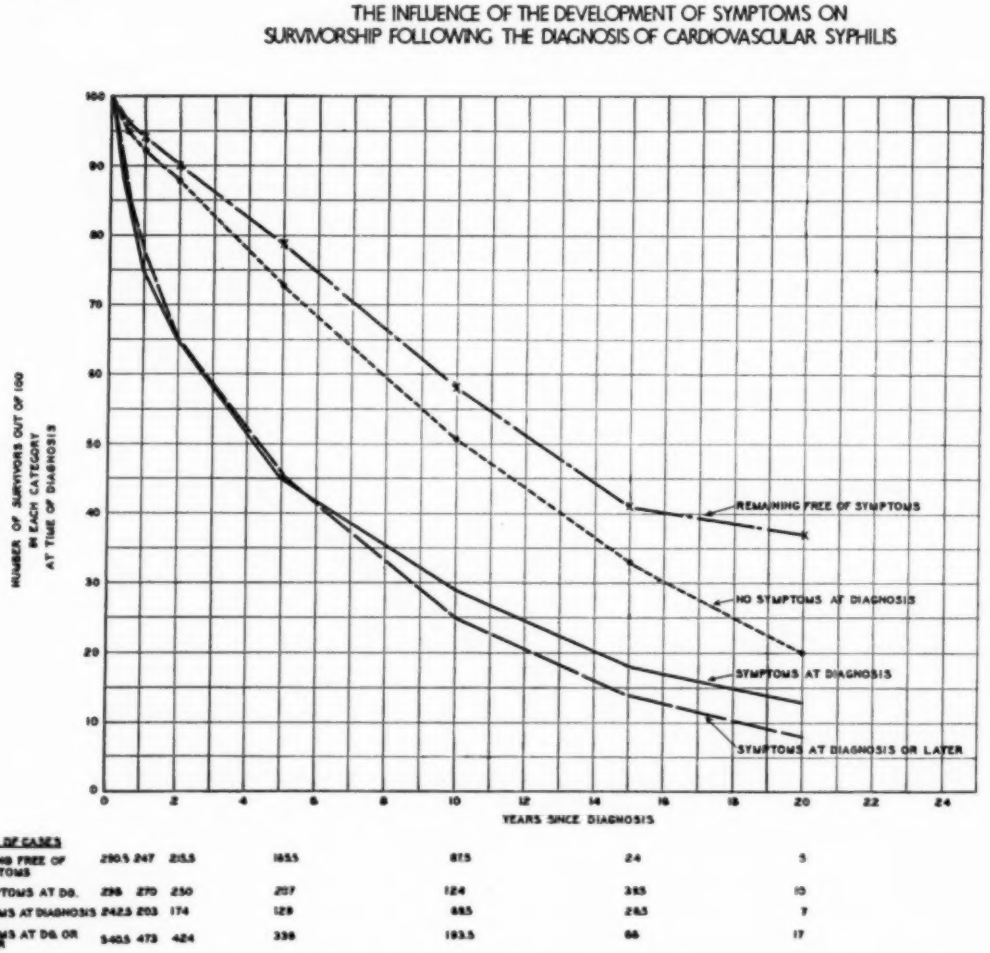
THE INFLUENCE OF THE DEVELOPMENT OF SYMPTOMS ON
SURVIVORSHIP FOLLOWING THE DIAGNOSIS OF CARDIOVASCULAR SYPHILIS
NUMBER OF SURVIVORS OUT OF 100
IN EACH CATEGORY
AT TIME OF DIAGNOSIS
REMAINING FREE OF SYMPTOMS
NO SYMPTOMS AT DIAGNOSIS
SYMPTOMS AT DIAGNOSIS
SYMPTOMS AT DIAGNOSIS OR LATER
YEARS SINCE DIAGNOSIS
NO. OF CASES
REMAINING FREE OF SYMPTOMS 290.5 247 215.5 165.5 87.5 24 5
NO SYMPTOMS AT DG. 256 270 250 217 124 38.5 10
SYMPTOMS AT DIAGNOSIS 242.5 203 174 129 88.5 26.5 7
SYMPTOMS AT DG. OR LATER 540.5 473 424 338 183.5 66 17

Fig. 7.—The influence of the development of symptoms on survivorship following the diagnosis of cardiovascular syphilis.

In Fig. 7 the survivorship has been compared for those patients who never had symptoms at any time, those who were free of symptoms at the time of diagnosis, those with symptoms at the time of diagnosis, and all those who had symptoms at any time, starting from the time at which they developed symptoms.

This last group included a number of patients who were free of symptoms at the time of diagnosis but who later developed symptoms.

The upper line in Fig. 7 represents the deaths among those patients who were free of symptoms at all times. It is, at first, startling to find out that 22 per cent and 59 per cent of those patients died in 5 and 15 years, respectively. It might be inferred that all such patients died of some intercurrent disease or suffered sudden death due to cardiovascular syphilis, in which the symptoms were agonal and did not come to the attention of the physician. However, in many cases, it had been possible to determine that a patient had died (from county clerk records and newspaper articles) without being able to obtain any facts about his clinical course. Some of these were patients who had been lost from clinic observation for years, and nothing was known of their clinical course since they were last seen in the hospital. These patients may have had symptoms due to cardiovascular syphilis which were unknown to the clinic physicians. They are here recorded as having been symptom free during the period of clinic observation, since more exact information was not available.

The second line from the top in Fig. 7 is of clinical interest, and indicates what may be expected of the patient found to have aortic insufficiency who is free of symptoms at the time of diagnosis whether or not he later develops symptoms. In 5 years, 73 per cent of such patients remain alive, while in 10 and 15 years there are still 51 per cent and 33 per cent, respectively, who survive. The third line indicates the prognosis to be expected from those who have symptoms when they are first seen. The survival is much less than in the first two groups; 45 per cent survive 5 years, and only 18 per cent are alive at the end of 15 years.

The lowest line permits assessment of the prognosis among individuals found to have symptoms at diagnosis or at any time thereafter. It is not greatly different from the curve confined to that group having symptoms for the first six years, but, thereafter, it drops below that group. This may be interpreted to mean that the survival curve for that group developing symptoms at some time after diagnosis is even poorer than for those who have symptoms at diagnosis. The reasons for this are not clear but may reflect some kind of selective process such as differences in therapy and advice with regard to work status which operates to produce a higher mortality in the former group.

Effect of the Development of Cardiac Failure on the Survival.—A consideration of the effect of congestive heart failure on the outcome of the disease, as presented in Fig. 8, shows even more startling differences in the prognosis.

Those patients who remained free of failure showed a very low mortality, as 56 per cent of them survived fifteen years. Those who were in failure at the time of diagnosis had a very poor prognosis. Less than 20 per cent survived five years and less than 6 per cent survived 10 years. Again, the lower line allows assessment of the prognosis of these patients who either were in failure at the time of diagnosis or when seen at some later date are found to have developed failure. The explanation for the relationship exhibited here is the same as that advanced for Fig. 8. The prognosis for the patients free of failure at the time of diagnosis, regardless of the subsequent course, was intermediate, about 30 per cent of them surviving ten years. This re-emphasizes the importance of failure in the course of syphilitic aortic insufficiency.

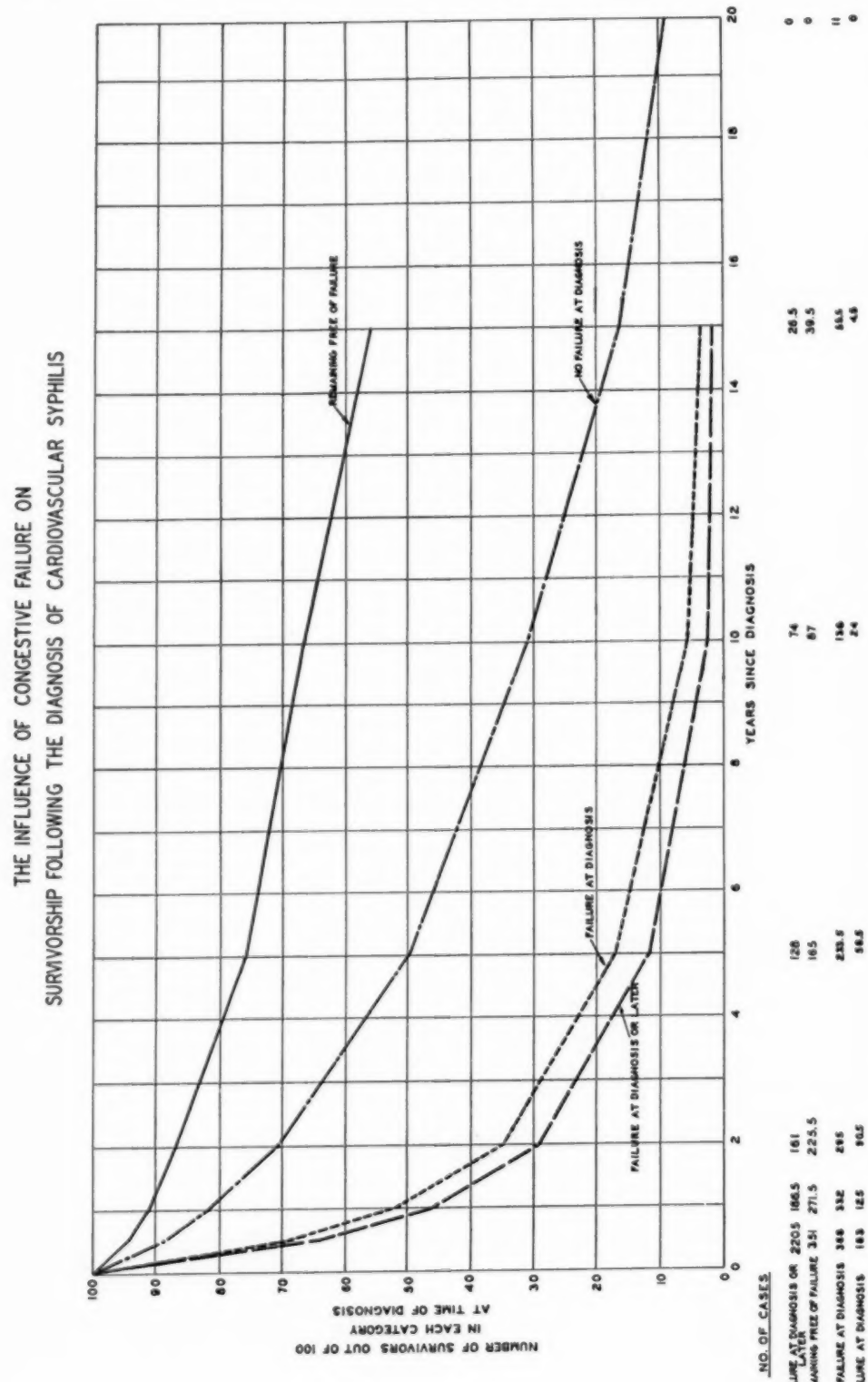
THE INFLUENCE OF CONGESTIVE FAILURE ON
SURVIVORSHIP FOLLOWING THE DIAGNOSIS OF CARDIOVASCULAR SYPHILIS
NUMBER OF SURVIVORS OUT OF 100
IN EACH CATEGORY
AT TIME OF DIAGNOSIS
REMAINING FREE OF FAILURE
NO FAILURE AT DIAGNOSIS
FAILURE AT DIAGNOSIS
FAILURE AT DIAGNOSIS OR LATER
YEARS SINCE DIAGNOSIS
NO. OF CASES
FAILURE AT DIAGNOSIS OR LATER 2205 166.5 161 126 74 28.5 0
REMAINING FREE OF FAILURE 351 271.5 225.5 165 67 39.5 0
NO FAILURE AT DIAGNOSIS 346 332 295 233.5 136 66.5 11
FAILURE AT DIAGNOSIS 183 125 90.5 66.5 24 4.5 0

Fig. 8.—The influence of congestive failure on survivorship following the diagnosis of cardiovascular syphilis.

Effect of the Development of Angina on Survival.—A similar analysis of the role of angina in the prognosis of those patients is presented in Fig. 9. The importance of this symptom lies in its relationship to the location of a plaque of syphilitic aortitis at one or both coronary ostia with the mechanical production of coronary insufficiency.

The same relationships exist, but they are less striking. The ten-year survival was 29 per cent for those remaining free of angina and 17 per cent for those who developed this symptom. Evidently angina, though important, is not as catastrophic a development as failure in these patients.

Effect of Treatment Prior to the Diagnosis of Cardiovascular Syphilis.—It was demonstrated in an earlier paper of this series that the patients receiving treatment for cardiovascular syphilis and those who had no treatment were so dissimilar in respect to many variables that no statistical comparison could be made which would give valid information as to the effect of treatment on the prognosis. This made it necessary to carry out the matching process indicated above, in which the "treatment" and "no treatment" groups were proportionately distributed so that their effect on other comparisons would be cancelled.

An attempt was made here, however, to evaluate the role of treatment prior to the diagnosis of cardiovascular syphilis in modifying the prognosis. Unfortunately the information was often incomplete. In some cases the treatment had been received many years before the development of cardiovascular syphilis, while in others it had been given only a year or so before aortic insufficiency had been discovered in a patient previously considered to have late latent or other noncardiovascular syphilis. The number of cases was too few to permit analysis in relation to duration of treatment.

Patients with a record of over 40 injections of a trivalent arsenic or over 2.4 million units of penicillin were considered to have had adequate treatment. Patients with less than this, including those treated with bismuth, were considered to have had slight treatment.

Figure 10 indicates the survival of this nondescript group of patients. It may be said, optimistically, that some treatment given at some time before diagnosis of cardiovascular syphilis may be better than no treatment, since the two treatment groups had a better survival than the patients who received no treatment, and the adequately treated group was better off than the group receiving inadequate treatment. The differences disappear after ten years; a fact which is not surprising, as it is likely that, ten years after the diagnosis of and treatment given specifically for the active cardiovascular syphilis lesions, the inflammatory component of the aortic lesion has become quiescent, and the clinical disease is expressed more in terms of scar tissue with a mechanically defective aortic wall, than by any active lesion.

Cause of Death Among the Patients not Autopsied.—Of the patients in this series, 632 died, 493 having been seen at Johns Hopkins Hospital and 139 at New York Hospital. In many cases the information surrounding their death was fragmentary and not accurate enough to be useful in determining the exact clinical cause of death.

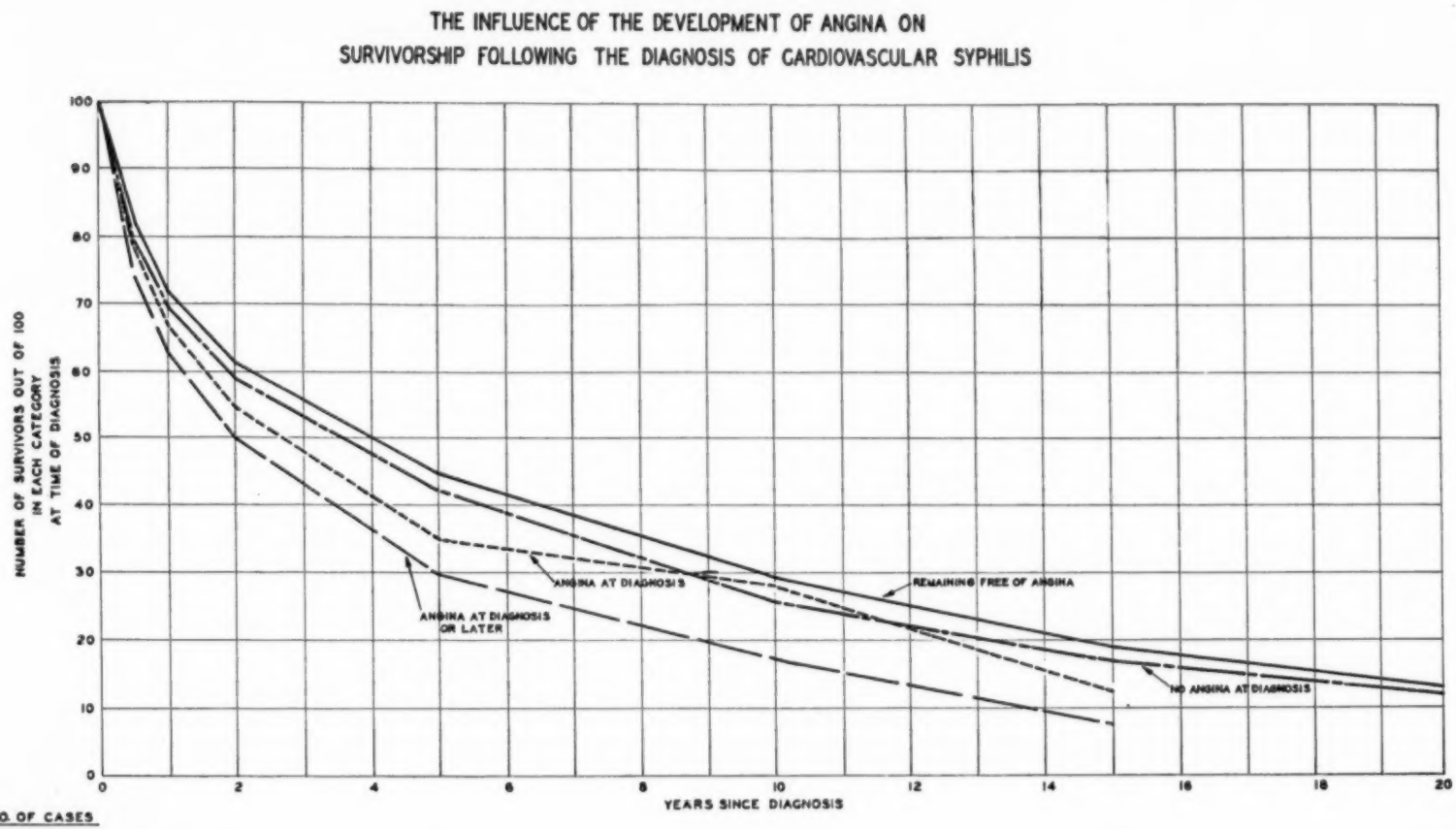
THE INFLUENCE OF THE DEVELOPMENT OF ANGINA ON
SURVIVORSHIP FOLLOWING THE DIAGNOSIS OF CARDIOVASCULAR SYPHILIS
NUMBER OF SURVIVORS OUT OF 100 IN EACH CATEGORY AT TIME OF DIAGNOSIS
YEARS SINCE DIAGNOSIS
ANGINA AT DIAGNOSIS OR LATER
ANGINA AT DIAGNOSIS
REMAINING FREE OF ANGINA
NO ANGINA AT DIAGNOSIS
NO. OF CASES
ANGINA AT DIAGNOSIS OR LATER 123.5 97 84 67 39 18 2.5
REMAINING FREE OF ANGINA 395.5 300.5 249.5 190.5 104.5 39.5 12.5
NO ANGINA AT DIAGNOSIS 402.5 311 263.5 207 118.5 45 13
ANGINA AT DIAGNOSIS 116.5 88.5 70 50.5 24 12.5 0

Fig. 9.—The influence of the development of angina on survivorship following the diagnosis of cardiovascular syphilis.

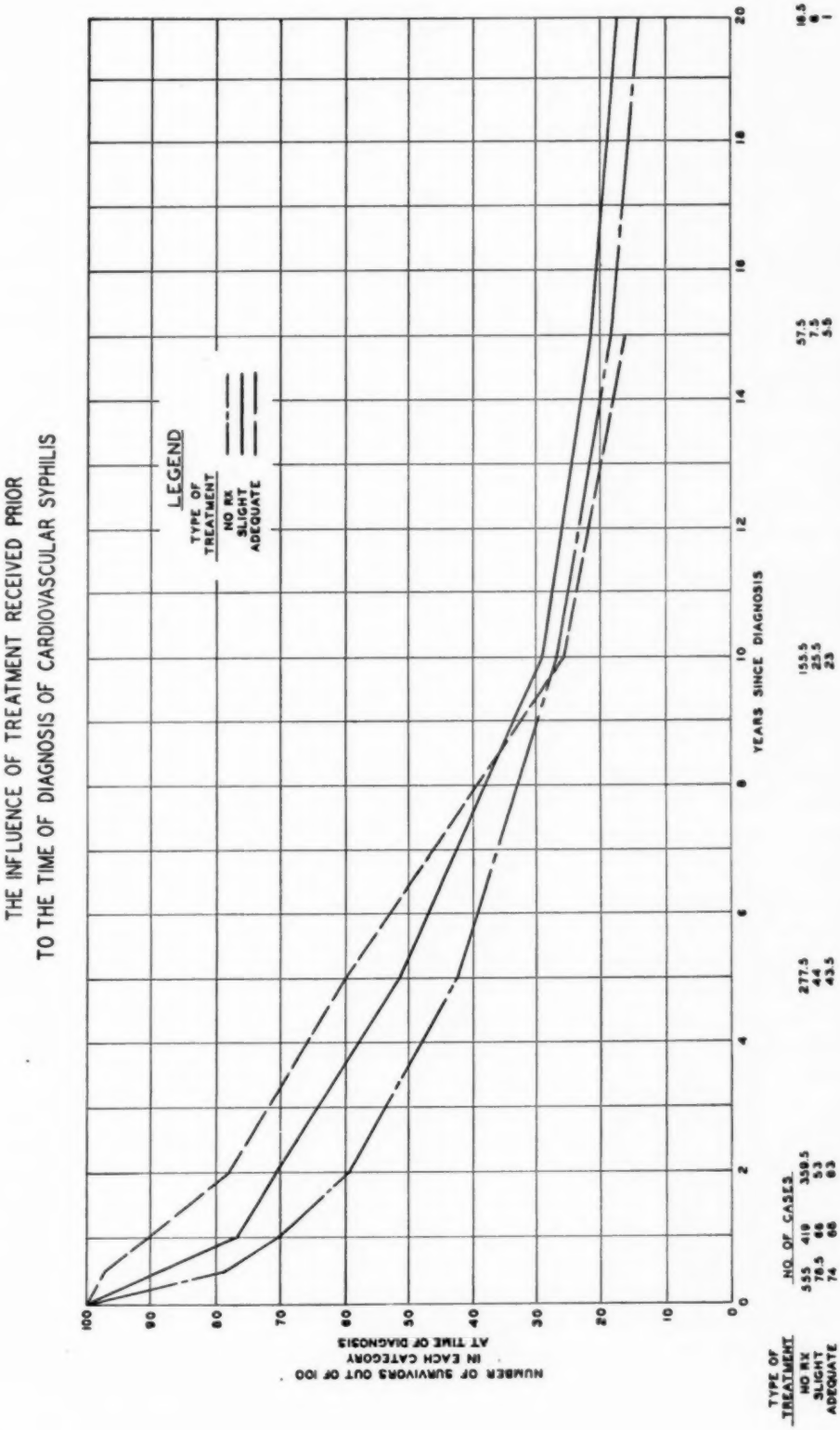
THE INFLUENCE OF TREATMENT RECEIVED PRIOR
TO THE TIME OF DIAGNOSIS OF CARDIOVASCULAR SYPHILIS
LEGEND
TYPE OF TREATMENT
NO RX
SLIGHT
ADEQUATE
NUMBER OF SURVIVORS OUT OF 100 IN EACH CATEGORY AT TIME OF DIAGNOSIS
YEARS SINCE DIAGNOSIS
TYPE OF TREATMENT
NO. OF CASES
NO RX 335 419 338.5 277.5 155.5 57.5 10.5
SLIGHT 78.5 66 53 44 25.5 7.5 1
ADEQUATE 74 68 63 43.5 23 5.5

Fig. 10.—The influence on treatment received prior to the time of diagnosis of cardiovascular syphilis.

In 413 of these patients, no autopsies were performed. Since all of the autopsied patients died in a hospital, they may have been a special group, possibly more impressively ill before death than the average patient. Therefore, the cause of death in this group may not have been representative of that for the entire group. To investigate further, comparison is made of the clinical cause of death, as gleaned from death reports or from description of the patients' terminal illness among the autopsied patients and among the nonautopsied patients. This is shown in Table V.

Because of the vague nature of the information obtained, it was only possible to categorize patients as probably having died of cardiovascular disease, having died of other causes, or having died without available record of type of clinical course.

It may be seen that for both the New York Hospital and for Johns Hopkins Hospital, about 75 per cent of the patients in each group died with symptoms of cardiovascular disease, whether they had been autopsied or not. This is rather tenuous evidence but may suggest a degree of similarity among the two groups in respect to cause of death.

Cause of Death in the Autopsied Patients.—Autopsies were done on 219 cases and the reports of these were collected, along with a summary of the clinical data. On these patients, accurate information as to the cause of death could be obtained. The data are summarized in Table VI. The patients classified clinically as dying of cardiovascular syphilis had this diagnosis listed as the cause of death. In a small group, syphilitic aortic insufficiency was not listed as the cause of death, but the patient's death was due to cardiac disease, and from the course it is reasonable to suppose that he died of cardiovascular syphilis. These are listed in Table VI as presumably dying of cardiovascular syphilis. The remaining group died primarily because of intercurrent disease.

The autopsy diagnoses of cardiovascular syphilis or of no cardiovascular syphilis are compared with the clinical cause of death. The autopsy diagnoses are further subdivided; first, into those with insufficiency alone and those with other cardiovascular disease (syphilitic such as aneurysm or osteal stenosis, or non-syphilitic, such as subacute bacterial endocarditis or rheumatic valvulitis); second, those with nonrelated disease, (cerebral hemorrhage, cancer, etc.); and third, those with aortitis alone. Of the patients without cardiovascular syphilis, there is a division of those with heart disease (hypertensive, arteriosclerotic, or rheumatic) and those with no evidence of cardiovascular disease.

In the total group 84.6 per cent and 81.9 per cent of the Johns Hopkins and New York Hospital patients, respectively, had autopsy-proved syphilitic aortic insufficiency. Of the New York Hospital group an additional 11.4 per cent had aortitis without demonstrable insufficiency. It is very likely that in life, with blood pressure acting on the damaged aortic walls, an early insufficiency did in fact exist without later presenting the pathognomonic signs of rolled aortic cusps and widened commissures. This is probably the type of patient often seen with early aortic insufficiency whose murmur entirely disappears after a few days of bed rest. It may be said that the clinical diagnosis was correct in 84.5 per cent of

TABLE V. COMPARISON OF THE CLINICAL CAUSE OF DEATH IN THOSE PATIENTS HAVING AND NOT HAVING AUTOPSIES

CLINICAL CAUSE OF DEATH	JOHNS HOPKINS HOSPITAL						NEW YORK HOSPITAL					
	PRESUMABLY CARDIOVASCULAR DISEASE		NOT CARDIOVASCULAR DISEASE		UNKNOWN		PRESUMABLY CARDIOVASCULAR DISEASE		NOT CARDIOVASCULAR DISEASE		UNKNOWN	
	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
Autopsied patients	141	80.7	34	19.4	0		33	75.0	11	25.0	0	
Nonautopsied patients	239	75.2	75	23.6	4	1.3	70	73.6	18	19.0	7	7.4

TABLE VI. COMPARISON OF THE CLINICAL CAUSE OF DEATH AND AUTOPSY DIAGNOSES

AUTOPSY FINDINGS	CLINICAL CAUSE OF DEATH							
	JOHNS HOPKINS HOSPITAL			NEW YORK HOSPITAL			TOTAL	
	CARDIO-VASCULAR SYPHILIS	PROBABLY CARDIO-VASCULAR SYPHILIS	NOT CARDIO-VASCULAR SYPHILIS	CARDIO-VASCULAR SYPHILIS	PROBABLY CARDIO-VASCULAR SYPHILIS	NOT CARDIO-VASCULAR SYPHILIS	JOHNS HOPKINS HOSPITAL	NEW YORK HOSPITAL
Aortic insufficiency only	51	2	2	9	4	3	55	16
Aortic insufficiency and other cardiovascular syphilis	43	0	2	7	1	0	45	8
Aortic insufficiency and other cardiovascular disease	17	2	5	4	1	4	24	9
Aortic insufficiency and other disease	7	0	17	2	0	1	24	3
Aortitis only	0	0	0	2	1	2	0	5
All aortic insufficiency and aortitis	118	4	26	24	7	10	148	41
Other cardiovascular disease	13	5	8	1	1	1	26	3
Other disease	1	0	0	0	0	0	1	0
All no aortic insufficiency and aortitis	14	5	8	1	1	1	27	3
Totals	132	9	34	25	8	11	175	44

the patients at Johns Hopkins Hospital and in 93.2 per cent of the patients at New York Hospital. In 15.5 per cent and 6.8 per cent, respectively, the diagnosis was in error.

Of the autopsied patients found to have had aortic insufficiency, 31.4 per cent and 36.4 per cent, respectively, at Johns Hopkins and the New York Hospital had aortic insufficiency alone while 25.7 per cent and 18.2 per cent had other evidences of cardiovascular syphilis. Of those who had no autopsy evidence of cardiovascular syphilis, only 0.6 per cent at the Johns Hopkins Hospital and none at the New York Hospital failed to have some other cardiac lesion.

The clinical cause of death among all the autopsied patients at Johns Hopkins and the New York Hospital was considered by the clinicians to be due to cardiovascular syphilis in 80.7 per cent and 75.0 per cent of the cases, respectively.

DISCUSSION

Different aspects of cardiovascular syphilis in the patients of this series have been explored in the preceding sections of this study. A discussion of some of the implications of these data is warranted.

When the study was originally instigated, two objectives were considered of special importance, and there has been constant emphasis on developing the data in such a way that it would throw light on them. The first objective was to explore the possibility of using case records from different clinics over a period of years in an attempt to discover whether or not treatment altered the course of cardiovascular syphilis. In the earlier papers of this study,[11,12] this was considered at length. It was found that not only were there marked dissimilarities between the two groups in the comparability and completeness of the materials in the past records, but that even within the same clinic the differences between the treatment groups and the nontreatment groups were so great that it was concluded that it was difficult, if not impossible, to use the data in past clinical records to evaluate a therapeutic procedure.

The second objective of the study as originally conceived was to discover whether the large volume of material in such past clinical records could be used to cast some light on the nature of cardiovascular syphilis, and, if so, how this might be done. The material presented in the present study is directed at this second purpose. It is concluded that one can obtain a picture of some of the influence of factors other than treatment on the course of the disease by employment of a matching process such as described in the body of the paper.

In connection with the follow-up of over one thousand patients in the study, it should be noted that approximately three-quarters of all the patients were followed throughout the study period or until time of death.

The need for some means of evaluating the influence on prognosis of factors other than therapy is indicated by the confusion which exists in the literature over such a basic fact as average length of survival following diagnosis. The question of over-all survival could be answered by simply listing the average time between diagnosis and death for those patients who died. However, this marked oversimplification gives a misleading result, as the many factors which alter the prognosis are grouped together. In order to get a more meaningful answer, a more

accurate definition of the material was carried out in respect to certain factors found to be of importance in determining the prognosis. This was achieved through the matching procedure described earlier, which allows an evaluation of the prognosis as affected by each of these factors. Because of inadequate numbers of patients for a complete analysis separately, sex and race were combined. Nevertheless, from the data obtained, it seems likely that they both play a role, particularly in the first five years after diagnosis, with Negro men having a poorer prognosis than Negro women or whites of both sexes. The differences are not marked and fail to support the usual clinical impression that sex and race are of paramount importance in estimating the prognosis. It may be that differences of the kind usually supposed to be present were due to other factors such as those controlled by matching in this study.

Whether or not the differences which were observed are due to racial and sex differences in host-parasite relationship cannot be said with certainty. In both New York City and Baltimore the majority of Negroes of either sex, but particularly the men, are manual laborers, and, job for job, do a heavier type of work. This, or some other unknown factor, might be the cause of the difference in prognosis in these different groups. An investigation of the role of work status in determining the prognosis was not fruitful because it, too, contained a hidden classification, in this case, the fact that the patients not doing heavy labor were prevented from it because of symptoms of cardiac failure.

This phase of the study, if it does little else, emphasizes the difficulty in analyzing even such clear-cut factors as race and sex in relationship to length of life. It seems that race and sex are intimately connected with work status. An investigation of the effect of work status demonstrates that it is inseparably entangled with economic factors that are undetermined in this study and with the severity of the illness, itself closely related to the over-all prognosis. Thus a circle of interrelated variables is discovered, in which the isolation of any one factor is quite unreliable. It should be re-emphasized that these variables, like the other ones investigated in this study, are "matched" in the subsequent investigation so that their effect is neutralized.

The life expectancy of these patients for each of a number of age groups compared with that for the population at large is important. That younger patients have a poorer prognosis than older ones, an often-made statement, is only true for the first five years after diagnosis, but thereafter the hazard is on the side of the elderly.

The most dramatic data presented above had to do with the development of symptoms or signs of heart disease on the prognosis. Angina, congestive failure, and "cardiac symptoms" were considered separately. Actually, they all are aspects of the same calamity, namely, the arrival by the patient at a point where his disease is advanced enough to intrude on his normal way of life. Failure is a serious complication, and its effect is more dramatic, but in the case of "symptoms" and angina, the effect, though less pronounced, was similar. It should be noted that many patients in this series, particularly in the older age groups, had concurrent hypertension and arteriosclerosis. In some cases the symptoms may have been associated primarily with one of these disease processes. What role

should be assigned to each element in such a patient would be a difficult and inaccurate guess at the clinical level, and no attempt was made to do this from the charts.

As has been noted, an attempt to evaluate the role of treatment prior to diagnosis was of no more value than the earlier effort to evaluate treatment given specifically for cardiovascular syphilis. The reasons are much the same, and the accuracy of the history prior to the time of diagnosis is open to question.

Of the 632 patients in this group who died, 413 did not have autopsies. Frequently very little was known about their clinical course during the last years of their life, but it was usually possible to learn enough about them to classify them as probably dying of cardiovascular disease or of other disease. This was done, and they were compared with the autopsied patients in whom accurate knowledge of the clinical course was available. In each case, about 75 per cent of the patients had died with cardiovascular symptoms. This suggests that the two groups may have been homogeneous in respect to cause of death. With this reservation in mind, the smaller group of autopsied patients was examined in greater detail. It was found that the great majority of them died with the diagnosis of cardiovascular syphilis as the clinical cause of death. The others died with the diagnosis of aortic insufficiency as a secondary or contributory cause of death. Of the patients in the autopsied group, syphilitic aortic insufficiency was proved in all but 15.5 per cent and 6.8 per cent of the patients at the Johns Hopkins and the New York Hospital, respectively. In the cases where the clinical diagnosis was not confirmed, rheumatic heart disease and calcific aortic disease were the most common diagnoses, in that order.

SUMMARY AND CONCLUSION

1. An investigation of the course of 1,020 patients with the clinical diagnosis of syphilitic aortic insufficiency followed in the Johns Hopkins Hospital and the New York Hospital for 20 years is presented.

2. Three-quarters of all patients in this group were followed throughout the study period or until the time of their death.

3. After an initial high risk of hospitalization, presumably associated with routine admission at the time of diagnosis, there is a steady incidence of hospitalization which does not change through the years. After ten years, 10 per cent and 21 per cent of the patients at the New York and Johns Hopkins Hospitals, respectively, not admitted at the time of diagnosis had subsequently one or more hospital admissions.

4. The long term prognosis for the patients in this group was good; 43 per cent and 33 per cent of the patients surviving 10 years and 30 per cent and 20 per cent surviving 15 years at the New York and Johns Hopkins Hospitals, respectively.

5. The effect of race and sex was difficult to evaluate and interrelate with the type of work performed and economic factors, but it was apparent that women did somewhat better than men and whites better than nonwhites (of which the great majority were Negroes.)

6. The effect of work could not be investigated reliably because of technical difficulties.

7. Age at the time of diagnosis has a less pronounced effect on the length of survival than is often thought. There is a slightly increased death rate in the patients under 40 years of age during the first five years, but thereafter the advantage is in favor of youth. Of the patients first seen when less than 40 years old, 35 per cent survived 10 years, whereas 21 per cent of those over 60 years at the time of diagnosis survived this period.

8. The survival of those patients free of symptoms at the time of diagnosis was much greater than those discovered at the time or of after the onset of symptoms. Fifty-one per cent of the former and 29 per cent of the latter group survived 10 years. Those free of symptoms at all times did better still, 58 per cent surviving 10 years. Of those originally free of symptoms who later developed them, 25 per cent survived 10 years from the time of their onset.

9. Similarly, of those patients free of failure at the time of diagnosis, 32 per cent survived 10 years and of those without angina at time of diagnosis, 26 per cent survived this time. The ten-year survival for those who had these two symptoms at the time of diagnosis was 6 per cent and 28 per cent, respectively.

10. The effect of treatment prior to or after the time of diagnosis could not be investigated reliably.

11. Of the patients who died, 75 per cent died with predominant symptoms of cardiovascular disease.

12. Of the patients autopsied, the diagnosis of syphilitic aortic insufficiency was substantiated in 93.2 per cent of those at the New York Hospital and 84.5 per cent at the Johns Hopkins Hospital.

APPENDIX

In the section on methodology, a general description of the matching process has been given. It has been stated that the matching process is essentially one of making the proportional distribution of several variables for which the matching is carried out the same in the two groups being compared. Thus, if A and B are the two groups being compared, and it is desired to make them comparable with respect to six variables at the same time, the proportional distribution of all six variables is made the same in the two groups.

In carrying out the process the matching was always done first with respect to treatment for cardiovascular syphilis. The question then arose as to which of the several remaining variables—age, race, sex, treatment prior to diagnosis, work status, and symptoms prior to diagnosis—to select as the one with which to continue the matching process. The question was answered by constructing a series of tables like that of Table I of the text distributing the two groups—in this case those without failure, 492, and those with failure, 423—against each of the five variables. (Race and sex were combined as one variable.) These tables were then examined by the chi-square test and a work table similar to Table A was drawn.

TABLE A

VARIABLES	X^2	d.f	P
Symptoms prior to diagnosis	194.551	2	.000000
Work status	32.222	1	.000000
Treatment prior to diagnosis	33.211	2	.000000
Age	5.165	3	.3916
Race and sex	13.074	3	.0046

After examining the X^2 and P values, the matching process was continued on that variable showing the smallest value of P, since the observed differences between the failure and no-failure groups were least likely to occur by chance in this group. For Table A, the variable was chosen as "symptoms prior to diagnosis." The proportional distribution of the "failure" and "no-failure" groups was then made the same with respect to this variable reducing the number in the two groups to 422 and 265, respectively. A new set of chi-square and P values was then determined for the remaining variables and the process repeated until all the variables were either perfectly matching on this proportional basis or showed P values well above the 5 per cent level. In this case the four variables, treatment for cardiovascular syphilis, symptoms prior to diagnosis, work status, and treatment prior to diagnosis were made proportionally the same in the two groups. For the remaining variables—age, race and sex—the P value for X^2 then became greater than 0.4.

As indicated in the test, this process yielded final numbers of 156 in the "no-failure" group and 422 in the "failure" group.

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Clinical Reports

ARTERENOL AS AN ADJUNCT TO THE TREATMENT OF PAROXYSMAL TACHYCARDIA

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THE SUCCESS of intravenously administered procaine amide (Pronestyl Hydrochloride*) is sometimes prevented by a progressive fall in blood pressure with increasing doses. In several recent patients with paroxysmal ventricular tachycardia we have been oblige to stop therapy when the pressure became as low as 70/50 mm. Hg. In one such case therapy with procaine amide was attempted twice and stopped each time because of severe hypotension. Because the patient's clinical condition was desperate it appeared urgent to abolish the arrhythmia. We therefore began a constant intravenous infusion of *l*-arterenol (Levophed, *l*-norepinephrine) to maintain the blood pressure, and were then able to give procaine amide in doses adequate to effect conversion to sinus rhythm.

CASE REPORT

A 74-year-old man was admitted to the hospital because of substernal discomfort, palpitation, and dyspnea of several hours duration. Physical examination revealed moderate dyspnea, orthopnea, and slight cyanosis. The heart rate was 190, regular, and blood pressure was 85/70 mm. Hg. The heart was moderately enlarged. There was no peripheral edema or pulmonary râles. Oxygen therapy was begun at once.

The electrocardiogram on admission revealed a regular tachycardia with widened QRS complexes of left bundle branch block contour. There was second degree retrograde (ventriculo-auricular) block, with one P wave for every three QRS complexes (Fig. 1, *A*).

Over a twenty-minute period 1,000 mg. of procaine amide was given intravenously. The ventricular rate gradually decreased to 130. The blood pressure had fallen to 60/? and therapy was stopped. These results and those of subsequent treatment are shown in Fig. 2.

During the next ten hours the patient received only oxygen and sedatives. The ventricular rate increased to 142 (Fig. 1, *B*), blood pressure 75/?. A second attempt to terminate the tachycardia with procaine amide was made, giving 1,200 mg. in twenty-five minutes; the blood pressure fell to 50/? and the ventricular rate to 110. At this point a transient rise of pressure to 70/? was effected with a 10 mg. dose of desoxyephedrine (Desoxyn) given intravenously. Two additional doses were without effect.

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*Procaine amide (Pronestyl Hydrochloride) was supplied by E. R. Squibb & Sons, New York. *l*-Arterenol (Levophed) was supplied by Sterling-Winthrop, Inc., Rensselaer, New York.

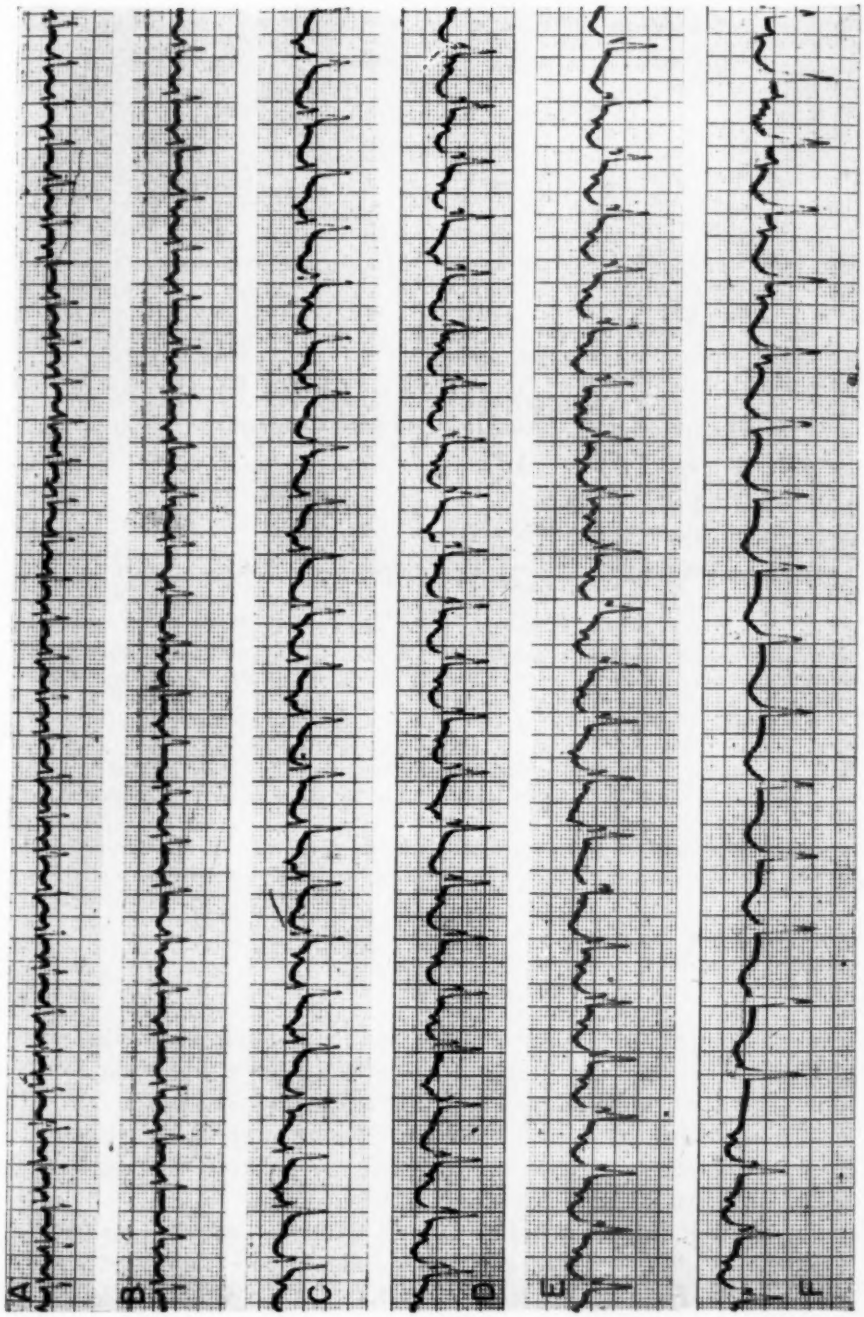

Fig. 1.—Lead V_1. *A*, Paroxysmal ventricular tachycardia, rate 175 after 200 mg. of Pronestyl Hydrochloride of first attempt. Retrograde ventriculo-auricular conduction 3:2. *B*. At beginning of second Pronestyl Hydrochloride trial, rate 140; retrograde ventriculo-auricular conduction is 3:2. *C*. After 800 mg. of Pronestyl Hydrochloride of second trial, rate 122; retrograde ventriculo-auricular conduction is 3:2. *D*. After 1,000 mg. of Pronestyl Hydrochloride of third trial, rate 120; retrograde ventriculo-auricular conduction is 5:4. *E*, After 1,500 mg. of Pronestyl Hydrochloride of third trial, rate 120; retrograde ventriculo-auricular conduction is 14:13. *F*, After 1,800 mg. of Pronestyl Hydrochloride of third trial, ventricular tachycardia is suppressed, a nodal tachycardia appears temporarily, and sinus rhythm is re-established.

An intravenous infusion of *l*-arterenol in physiologic saline was begun at a rate of 1.0 c.c. (4 micrograms of base per c.c.) per minute. Within five minutes the blood pressure had risen from 60/? to 90/60 mm. Hg. While continuing the infusion of *l*-arterenol, procaine amide was again given intravenously, but with no fall in blood pressure. After 1,800 mg. the ventricular

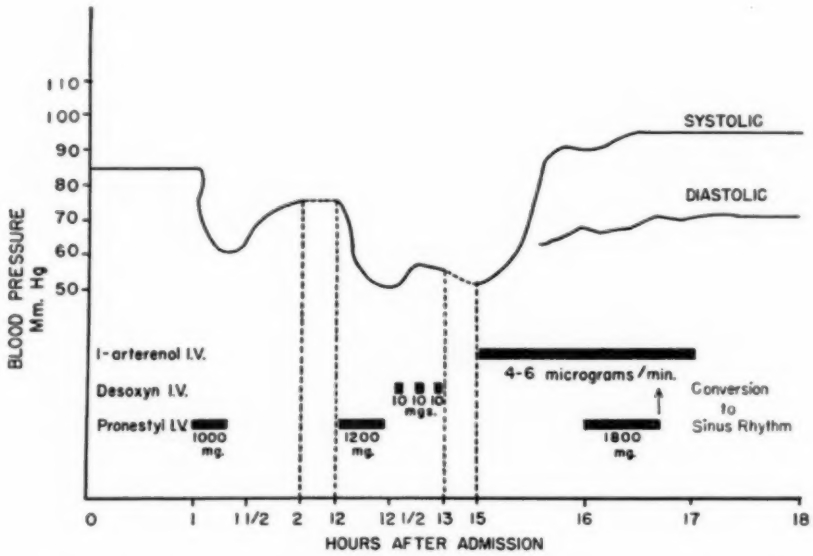

Fig. 2.—Blood pressure changes during treatment. Where not recorded, the diastolic pressure could not be determined because no sounds were audible over the brachial artery. At those times systolic pressure was determined by the palpatory method.

ectopic focus was suppressed, nodal rhythm appeared temporarily, and sinus rhythm became established (Fig. 1, *F*). The electrocardiogram then revealed evidence of recent anterior myocardial infarction.

The blood pressure remained at 100/70 mm. Hg after stopping the administration of *l*-arterenol. Sinus rhythm was maintained with 1 Gm. of procaine amide given orally four times daily for three days.

The patient then suddenly expired. An autopsy was not permitted.

COMMENT

The intravenous infusion of *l*-arterenol effectively maintained adequate blood pressure and permitted the simultaneous intravenous administration of procaine amide in amount adequate to effect conversion to sinus rhythm.

Because *l*-arterenol has been used in the treatment of shocklike states of cardiac origin following acute coronary occlusion,[1] it was believed relatively safe to use *l*-arterenol in the presence of paroxysmal tachycardia.

Without the pressor drug, doses of 1,000 and 1,200 mg. of procaine amide were the largest that could be given because they induced potentially dangerous levels of hypotension without the desired therapeutic effect. When an adequate blood pressure level was induced and maintained by *l*-arterenol, an effective dose of procaine amide was given, which was 50 per cent greater than the maximum dose tolerated previously.

We have successfully used *l*-arterenol in this manner to combat the hypotension due to procaine amide in two additional cases of ventricular paroxysmal tachycardia, in two cases of nodal tachycardia, and in two cases of auricular flutter with bundle branch block.

SUMMARY

The use of *l*-arterenol is described for maintaining adequate levels of blood pressure during the treatment of paroxysmal tachycardia with intravenous procaine amide. This measure appears to permit the use of larger doses of procaine amide than could otherwise be tolerated and thus facilitates termination of the paroxysm.

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CALCIFIED VENTRICULAR ANEURYSM

Case Report, With a Note on Prognosis

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CALCIFICATION in a cardiac aneurysm or an area of healed myocardial infarction is well known. Nevertheless, with the exception of the early cases of Corvisart,[1] Cruveilhier,[2] Thurnam,[3] and Legg,[4] only thirty-seven further cases of myocardial calcification have been reported during the present century. In twenty-six patients, the calcification occurred in a ventricular aneurysm;[5,20] in the remaining eleven patients, no aneurysm was demonstrated.[21,23] The patient with calcified ventricular aneurysm, presently reported, lived somewhat longer than the other published cases. The apparent longevity of these patients will be discussed.

CASE REPORT

H.L., a Russian-born tailor, had always been well until, in 1933, at the age of 54, he suffered an attack of coronary thrombosis. He was bedridden for five weeks. He had no subsequent anginal pain. In 1941, he was treated at Mount Sinai Hospital for a nonputrid lung abscess following bronchopneumonia. At that time, the heart sounds were reported as being of good quality, with a slight apical systolic murmur; blood pressure 115/70 mm. Hg; the chest roentgenogram showed slight cardiac enlargement to the left with bulging of the left ventricular contour and a slight calcification in that area; the possibility of ventricular aneurysm was considered. A duodenal ulcer was diagnosed in 1946. In 1949, he was confined to bed for three weeks because of a transient attack of angina pectoris. Later in 1949, he was readmitted to Mount Sinai Hospital because of bleeding from a duodenal ulcer. In April 1952, the patient, now age 73, was examined at the Research Department of the Sidney Hillman Health Center. He had kept in excellent health since 1949, was entirely without symptoms, and worked full-time as a fitter. There were no abnormalities on physical examination except for a distant first heart sound; the blood pressure was 130/95 mm. Hg. The chest roentgenogram showed calcification in the aortic knob and a ventricular aneurysm containing a well-defined calcified plaque (Fig. 1), in keeping with Sossman's[24] diagnostic criteria of cardiac calcifications. A lateral flat plate of the abdomen showed irregular calcifications in the aorta. The electrocardiogram showed inversion of the T waves in Lead 1 and Leads V_3 to V_6 and deep Q waves in leads V_3 to V_6. The total serum cholesterol was 209 mg. per cent, serum phospholipids 222 mg. per cent, uric acid 5.9 mg. per cent; blood sugar and urine were normal. At the time of reporting (February 1953), the patient continues to be without symptoms.

COMMENT

The capacity for hard work of patients with aneurysms has been pointed out.[25] The longevity of patients with calcified aneurysm has also been stressed.[12,16]

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I have collected all published cases to try to determine the prognostic significance of myocardial calcifications even though it is evident that data collected from different sources by different means are not strictly comparable[26] and can only yield the roughest guide to prognosis.

A definite history of coronary thrombosis was obtained in fifteen cases of calcified aneurysm reported in the literature. Four of these were still living 8, 10, 15, and 18 years, respectively, after the acute attack;[5,11,12,16] the patient reported here survived 20 years. Seven patients died 5, 6, 6, 6, 9, 10, and 11 years, respectively, after the acute attack.[6,7,14,20]

Fig. 1.

These survival figures may be compared with those for patients with aneurysms without calcification, excluding those who died within a year after an attack of coronary thrombosis and thus had no reasonable chance to develop calcifications. Of fifteen such patients still living, four were alive after 2 years, ten after 5 years and one after 6 years.[5,10,25,27] Thirty-six patients with uncalcified aneurysm were followed until the time of their death; eleven died within 2 years, nineteen within 2 to 5 years, and six within 5 to 9 years.[5,10,25,28] The relatively greater longevity of patients with calcified aneurysm is apparent.*

Similarly, survival figures for patients with myocardial calcifications without aneurysm may be compared with the over-all prognosis of coronary thrombosis.

*The ages of patients with calcified aneurysms ranged from 31 to 80 years (mean 59 years); one patient was a woman. The corresponding age range for patients with aneurysms without calcification was 39 to 79 years (mean 56 years); a few of these patients were women.

Four patients with myocardial calcifications who are still alive survived 7, 7, 11, and 14 years respectively;[6,22] two patients died 10 years after the acute attack.[6,21] It is not usual for patients to be alive ten years after a coronary thrombosis[29-32] though it is by no means uncommon.[33] It would again appear that patients with calcifications live longer.

The question arises why the presence of calcification should be associated with relative longevity. A causal relationship, though suggested, appears unlikely. It is difficult to see how calcification could avert death by any mechanism other than the prevention of aneurysmal rupture, an exceedingly uncommon event.[34,35] Patients with calcified aneurysms apparently are those who survive long enough to develop calcification, the prognosis of patients with cardiac aneurysms depending on the state of the myocardium rather than on the presence of the aneurysm.[10,28] Similar reasoning may be applied to calcified myocardial scars without aneurysm. This interpretation would be supported by the fact that no instance of calcification has been reported less than 5 years after a coronary thrombosis. One patient, serially studied, had no radiologically demonstrable calcification as late as 7 years after a "heart attack"; calcification was first noted 9 years after the original attack.[11]

Though it is likely that the chances of calcification taking place in damaged tissue are greater the longer the patient lives, age is probably not the only factor involved. It is well known that atheromata differ in their degree of calcification. Many myocardial scars of long standing undoubtedly do not calcify. Calcification apparently takes place more readily in some individuals than in others. The mechanism of calcification in damaged or necrotic tissue remains unknown.

SUMMARY

The case is presented of a man aged 73, clinically well, who on roentgenogram examination exhibited a large calcified cardiac aneurysm, the end result of a myocardial infarction at the age of 54. A brief discussion of the literature is presented, particularly with reference to prognosis.

The author wishes to thank Dr. Ernst P. Boas for his encouragement and advice

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Announcement

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital by Louis N. Katz, M.D., (Director of the Cardiovascular Department, Medical Research Institute) and associates. The class will meet each day from 9:00 A.M. to 5:00 P.M., from August 3 through August 15.

Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Rivian H. Lewin, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

Review of Recent Advances

ASPECTS OF CARDIAC HYPERTROPHY

ROBERT P. GRANT, M.D.

BETHESDA, MD.

THE heart may increase its ventricular muscle mass as much as six times and, with this, is capable of increasing its effective work as much as twenty times—a remarkable instance of versatility among driving systems and one of the most dramatic physiologic adaptations of the human body. In addition, cardiac hypertrophy is one of the most common and important adaptations of the heart to disease. Yet, curiously enough, the mechanism for either the increase in strength or the increase in size in hypertrophy are largely unknown and have attracted remarkably little basic research. In the past generation, which has seen hundreds of responsible contributions on many aspects of cardiac physiology, there have not been five basic studies of the dynamics of cardiac hypertrophy.

Most clinicians look upon cardiac hypertrophy as a "natural" consequence of increased work by the heart in much the same way as they once regarded aging as a "natural" consequence of chronology and, therefore, not susceptible to research or inquiry. That this point of view may be unwarranted is perhaps best illustrated by pointing out that it has not yet been proved that the hypertrophied myocardial fiber is stronger than the normal fiber. Indeed, it is apparent from experimental literature that the normal heart is capable of as great strength of contraction as is produced ordinarily by the experimentally hypertrophied heart, and it can be shown by simple calculation that this is also true of the human heart, for with strenuous exercise the cardiac work per unit of time may exceed that required of the heart in a patient with severe essential hypertension and cardiac hypertrophy. As far as strength of an individual contraction is concerned, when all the energy of contraction is converted into pressure, as by occluding the aorta of a dog, the pressure within the left ventricle may exceed 300 mm. Hg and will go even higher if adrenalin has been administered; this is considerably higher than is encountered in experimental hypertension where cardiac hypertrophy is always present.[1-4]

But, it might be argued, these are all acute experiments and perhaps the role of hypertrophy is to make possible the maintenance of increased work or pressure over long periods of time. However, if this should prove to be the case, it would

From the Clinic of General Medicine and Experimental Therapeutics of the National Heart Institute, Section of Cardiodynamics, U. S. Public Health Service Hospital, Baltimore, Md.
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mean that the hypertrophy does not increase the strength of contraction but instead supplies some metabolic or energy substratum to accommodate to the increased work; in other words, the hypertrophy is a *consequence* of increased work but not directly its *source*.

There has been only a single study where the dynamic properties of the hypertrophied heart were compared with those of the normal heart.[5] In these experiments heart-lung preparations were used, and the work-capacity reserve of the normal and experimentally hypertrophied heart were compared in acute experiments. While the hypertrophied heart showed an increased reserve capacity for work, the difference was not great. Furthermore, it was impossible to evaluate the role of other factors which might increase heart work of the hypertrophied heart such as its greater diastolic size. A more crucial type of experiment where isolated strips or fibers of normal and hypertrophied myocardium are compared for their dynamic and metabolic properties has apparently never been performed. Indeed, such studies have not even been done of skeletal muscle hypertrophy which is all the more remarkable considering the importance of skeletal muscle hypertrophy in enterprises as far afield from medicine as athletics, troop training, horse racing, cattle breeding, etc.

Not only does it remain to be proved that hypertrophy endows cardiac muscle with greater strength of contraction, but there have even been opinions among workers in this field that hypertrophy is actually a "pathologic" and deleterious consequence of increased work by the heart.[6-9] One reason for this suggestion has been the abnormal ST-T component in the electrocardiogram in cases of marked left or right ventricular hypertrophy, for the abnormality closely resembles that seen in experimental and clinical coronary insufficiency. It has been suggested that these electrocardiographic changes mean that the muscle mass has outstripped its coronary supply, and the hypertrophy creates a condition of chronic coronary insufficiency.[10] Although most workers in this field believe that other explanations for the ST-T segment abnormality of ventricular hypertrophy are more plausible, these latter explanations are unproved, and there is no question that the number of capillaries per unit of cross-section area of the myocardium is decreased in ventricular hypertrophy.[11,12]

Another piece of evidence, that has been believed to indicate that hypertrophy is deleterious, is to be found in certain cases of idiopathic myocardial hypertrophy.[13] These patients, usually relatively young, develop congestive heart failure, and at autopsy no abnormality is to be found other than marked left ventricular hypertrophy. It is suggested that hypertrophy of the heart caused the failure in these cases. However, it is altogether possible that some yet unrecognized factor caused the heart failure and the hypertrophy was actually an ameliorating adaptation by the heart. Furthermore, there are a few patients with idiopathic hypertrophy, seemingly identical to the above patients, in whom no signs or symptoms of congestive heart failure preceded death; in one of these the heart weighed 1,100 grams at autopsy.[14,15] In addition there are a few patients with marked left ventricular hypertrophy which was not "idiopathic" where also there had been no evidence of heart failure up to the time of death.

A twenty-year-old man is reported who fell dead on a dance floor with no prior symptoms of congestive heart failure and at autopsy proved to have aortic stenosis and a heart weighing 2,300 grams, one of the heaviest hearts in recorded medical history.[16] The hypertrophy cannot have seriously impaired heart function in these instances.

Although it may be unlikely that hypertrophy is deleterious for cardiac function, it is nevertheless difficult to prove that the clinical course of a patient with heart disease is significantly improved by the presence or development of hypertrophy. For example, there is a small group of patients with marked hypertension and congestive heart failure who at autopsy show little or no hypertrophy; yet the severity of the hypertension, degree of heart failure, and duration of illness are not substantially different in these patients from those who show marked left ventricular hypertrophy at autopsy.[17-20]

Another perhaps more clearly defined test for an ameliorating effect of hypertrophy is to be seen in the clinical course of patients without heart disease who have some sudden cardiac accident which suddenly, but not progressively, increases the work of the heart tremendously. Examples of this would be the cases of spontaneous rupture of a normal aortic cusp, mitral leaflet, or papillary muscle; perforation of a dissecting aneurysm of the aorta or aneurysm of the sinus of Valsalva into another chamber of the heart; traumatic rupture of the interventricular septum in an otherwise normal heart, etc. In those rare instances where the subject survived the initial catastrophic event, congestive heart failure uniformly appeared in the second or third week after the accident, and the patient died weeks or occasionally months later, showing marked cardiac hypertrophy.[21,29] In these patients the need for greater heart work was presumably as great at the time of the accident as at any subsequent time. Accordingly, if the development of hypertrophy (which probably takes two to five weeks[30]) "improved" cardiac function, these patients should have had their greatest disability during the first few weeks and, with the development of the hypertrophy, should have improved clinically. However, this sequence has never been described and the downhill course was apparently not significantly influenced by the gradual development of hypertrophy in any of these patients.

These points are raised not because of a conviction that hypertrophy is not a source of increased strength of contraction by the heart, but to indicate that some of the widely accepted attitudes regarding cardiac hypertrophy deserve careful investigation and may require revision. The study of the properties of cardiac hypertrophy may well prove to be an extremely fruitful area for clinical and experimental investigation of heart disease.

There is another aspect of cardiac hypertrophy which, although not as controversial, is just as important and has been quite as neglected in cardiovascular research. This is the recognition that hypertrophy, whether of cardiac or skeletal muscle, is a particular type of tissue growth, and, like other examples of special growth, must depend upon certain highly specific enzymic, metabolic, and perhaps hormonal factors in order to take place. Conceivably the search for and study of these factors might lead to the discovery of pharmacologic methods for accelerating or inhibiting cardiac hypertrophy, which could be of great importance in the therapy of heart disease.[31,32]

This aspect of hypertrophy has important clinical implications in still another regard for there may be one or another form of heart disease which is partially or even completely due to a disorder of the metabolic substratum of the hypertrophy mechanism. Perhaps a disease of the heart now classified as "myocarditis" or "arteriosclerotic heart disease" is an example of this, for it is well recognized that in certain cases of myocarditis and what is called arteriosclerotic heart disease where congestive failure is present indicating a need for greater heart work, the heart at autopsy may be dilated but show little or no increase in weight.[33-35] Whatever the mechanism for the heart failure in these cases, something appears to have inhibited the hypertrophy process from taking place.

The morphologic aspects of cardiac hypertrophy have been recently reviewed elsewhere.[36] However, an important question concerning the anatomy of cardiac hypertrophy is: What limits it? Why does it not go "on and on" since in most heart diseases the need for greater heart work is believed to steadily increase? Does the individual with aortic stenosis or hypertension finally go into essentially irreversible congestive failure because the heart has, at a certain size, reached the limit of its capacity to hypertrophy? Or is it because the ameliorating effect of the hypertrophy begins to diminish as the heart approaches a certain degree of hypertrophy and the patient develops congestive heart failure when this degree of hypertrophy is exceeded?

That there is an anatomic "limit" to cardiac hypertrophy has been widely accepted among pathologists.[37] This is based upon the belief that in cardiac hypertrophy there is an increase in the diameter of the myocardial fibers but no increase in their number, and that some physical factor limits the extent to which the fiber diameter may increase.[38,39] However, the recent studies of Linzbach, which are certainly the most comprehensive and reliable yet performed in this difficult field, indicate that this may not be the case. Within the range of variations in heart size which may be attributed to differences in body exercise, there is probably no increase in the number of fibers and only an increase in fiber diameter. This "physiologic hypertrophy" may be seen in hearts up to 500 grams in weight, whether due to body exercise or to heart disease. Beyond this weight the thickened fibers split longitudinally producing a net increase in the number of fibers. Presumably with greater hypertrophy these daughter fibers and segments of fiber also increase in diameter and at critical widths split.[9,16] The importance of this contribution lies in the fact that, although the fibers are morphologically similar in "physiologic" and "pathologic" hypertrophy, the dynamic and metabolic properties of the fibers may well be different in these two stages of hypertrophy, and both will have to be studied before it can be decided to what extent hypertrophy is "good" or "bad" for cardiac function. It has been suggested that in most studies of experimental cardiac hypertrophy "physiologic" hypertrophy has not been exceeded.[40]

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Book Review

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KRE SLAUFFORSCHUNG. Hauptthema: Elektrokardiogramm. Darmstadt, 1952, Dr. Dietrich Steinkopff, Verlag. Vol. 18, pp. 334. Pr. DM 40.

This volume, containing thirty-eight electrocardiographic papers together with the discussions presented at the eighteenth meeting of the "Deutsche Gesellschaft für Kreislaufforschung," is an excellent cross section of the present work and thought in German electrocardiography. In general, the standard of most communications is impressive. One notes with a certain degree of satisfaction that electrocardiography in Germany is as controversial as in this country, if not more so. However, much of the controversy is centered on different problems, for instance, the compatibility of vector analysis with the "difference theory." This theory assumes that the electrocardiogram can be explained as the difference of two monophasic action currents of opposite polarity and slightly different phase from two different parts (or areas) of the heart. It has never found serious consideration in this country as a basis of electrocardiographic interpretation and, in the opinion of this reviewer, is open to objections even in its latest modifications by Schütz and Rothschuh (see book review "Rothschuh: Elektrophysiologie des Herzens, AM. HEART J. 45:315, 1953). Particularly, it appears that it cannot be easily reconciled with the concept of integrated spatial vectors. Surprisingly enough, the adherents of the "difference theory" (Schütz, Rothschuh, Weber) maintain that both concepts are compatible, that they constitute simply different aspects of the same phenomenon. This can be said, of course, for any method of analysis or interpretation concerned with the surface electrocardiogram.

Schaefer points out that vector analysis is a quantitative method, while the difference theory affords only a qualitative description. There is no need to go into details of this controversy in view of the limited interest in the difference theory in American electrocardiography.

The main presentations are those by Schaefer on the theoretical basis of the electrocardiogram (pp. 12 to 41), and by Holzmann (Clinical electrocardiography, pp. 120 to 140). In nearly all papers of that meeting reference is made to one or the other hypothesis advanced by Schaefer, either affirmative or controversial. It can be said, therefore, that Schaefer's paper is the central topic of discussion. It is an excellent condensation of his book "Das Elektrokardiogramm" (reviewed AM. HEART J. 43:157, 1952), but contains also some new experimental material.

In comparison with comparable meetings of American societies, a much greater part (about 50 per cent) of the papers is concerned with vector analysis, including analysis of area vectors in ten papers. In other words, the experimental and discussion material on the ventricular gradient presented at that meeting is very substantial compared to the recent American literature.

The opinions about the value of this method, however, are sharply divided; in no other country has the ventricular gradient found such emphatic proponents (H. Schaefer) and such outspoken criticism (Schlomka, Holzmann, Welsch and Spang). The objections are concerned with clinical usefulness rather than with the theoretical background, but it is agreed that the ventricular gradient may add important information in a few conditions such as the analysis of the orthostatic reaction (Gladewitz and Berg, p. 107), low voltage (Uhlenbruck, p. 160) and constrictive pericarditis (Schölmerich and Heberer, p. 215).

One of the difficulties in presenting the results of spatial vector analysis is the limitation of the publishing medium to one plane. In most publications in this country, the projections of spatial vectors or loops on three planes (horizontal, frontal, sagittal) are shown. This presentation is not satisfactory, because it is still necessary to visualize or synthetize the spatial vectors from these projections. From this point of view, the presentation of spatial vectors as done by Holzmann (p. 136), Bayer and Effert (p. 182), Gillmann (p. 184), and Portheine (p. 196) represents definite progress and appears to be superior, in certain aspects, to Grant's procedure.

Because of the limited space of this review, only a few arbitrarily selected examples of results can be given. Polzer (p. 91) demonstrates remarkable differences in the loop projections in the

frontal, sagittal, and horizontal plane when the leads of Duchosal, Milanovich, Wilson and Conway, Schellong, and Polzer and Schuhfried are compared. Schuhfried (p. 94) confirms these results in animal experiments where an artificial dipole was introduced into the dog's heart through a catheter. Wenger (p. 112) finds the formation of a double QRS loop ("Doppelschlingenbildung") in the horizontal and sagittal plane to be an important feature of right bundle branch block and stresses the value of spatial vector analysis for differentiation between this condition and right ventricular preponderance. With the development of left ventricular hypertrophy, an increasing portion of the QRS loop moves above the horizontal null plane, and at the same time its shape changes from oblong to circular, together with a reversal of the direction of rotation (Portheine, p. 196). Effert (p. 201) applies spatial vector analysis to the P wave; increased load of the left auricle increases the P vector and turns it farther to the left and back, while increased load of the right auricle turns the vector into the opposite direction. Bayer and Effert (p. 179) note a parallelism between mean QRS and T vector changes and pulmonary arterial pressure in right ventricular preponderance.

Exercise tolerance tests have been used in Germany for a long time and on a rather large scale; it is not surprising, therefore, that Holzmann discusses this important functional test at some length. In his experience, the exercise test shows an abnormal response in 90 per cent of patients with coronary artery disease, but whose electrocardiograms in rest were normal. This seems to be very optimistic, but such optimism is shared also by some American authors. On the other hand, Holzmann warns against the use of ergotamine in exercise tests for the purpose of differentiating between organic disease and functional heart disturbances. This was suggested first by Nordenfeldt (1941) and recently by Master and associates (Circulation **1**:692, 1950). Holzmann found that ergotamine may temporarily reverse the direction of abnormal T waves in healing or healed myocardial infarcts.

Kemmerer (p. 219) studied the protective value of nitrites and strophanthin in experimental coronary insufficiency produced by anoxia, using as criterion S-T and T-wave changes. The protective value of 0.2 Gm "Deriphyllin" or "Euphyllin" was greater than that of 0.4 Gm (intravenous administration), and equivalent to oral administration of 3 Gm. "Strophoral" (Strophoral contains 90 per cent strophanthine).

Uhlenbruck (p. 160) found no evidence of heart disease in 21 per cent of 177 cases of low voltage, which agrees with similar experience in this country. The ratio of the P-area vector to the QRS-area vector was valuable for the differentiation between normal and abnormal low QRS voltage, and Uhlenbruck suggested a ratio of 1.0 as critical.

Autopsy evidence reveals that an absent R wave does not necessarily indicate a transmural infarct, since it was found in infarcts where up to 40 per cent of the myocardial wall was not involved (Heinecker, p. 223). Schlomka (p. 165) presents some new evidence for his old hypothesis that in cardiac decompensation the QRS axis changes in the direction opposite to the ventricle primarily involved, i.e., to the right during failure primarily of the left heart (hypertension), and to the left in failure primarily of the right heart (mitral insufficiency).

Hegglin (p. 149) found in all conditions of shortened Q-T interval he studied (anoxia, monoiodine acetate, digitalis, hypercalcemia), a decrease of the adenosine triphosphate content in the heart.

The importance of neurogenic factors has always been stressed in the German literature and was discussed at this meeting by Holzmann and by Mueller (p. 237). However, when Schennetten (p. 189) claims that the reflex stimulus elicited in sensitive cardiac patients just by putting the electrode on the chest may produce a myocardial infarct, this is stretching things a bit too far.

From a technical point of view it is of interest that in nearly all of the numerous illustrations the electrocardiograms were taken with multichannel machines.

At the end of his paper, Spang refers to Wilson's well-known statement about the great deal of harm which is done, on a rather wide scale, by a false diagnosis of heart disease from electrocardiographic misinterpretation. He suggests that Wilson would have come to the same conclusion in Germany as in the United States. This is consolation (or desperation) on an international scale.

E.S.